10/510500

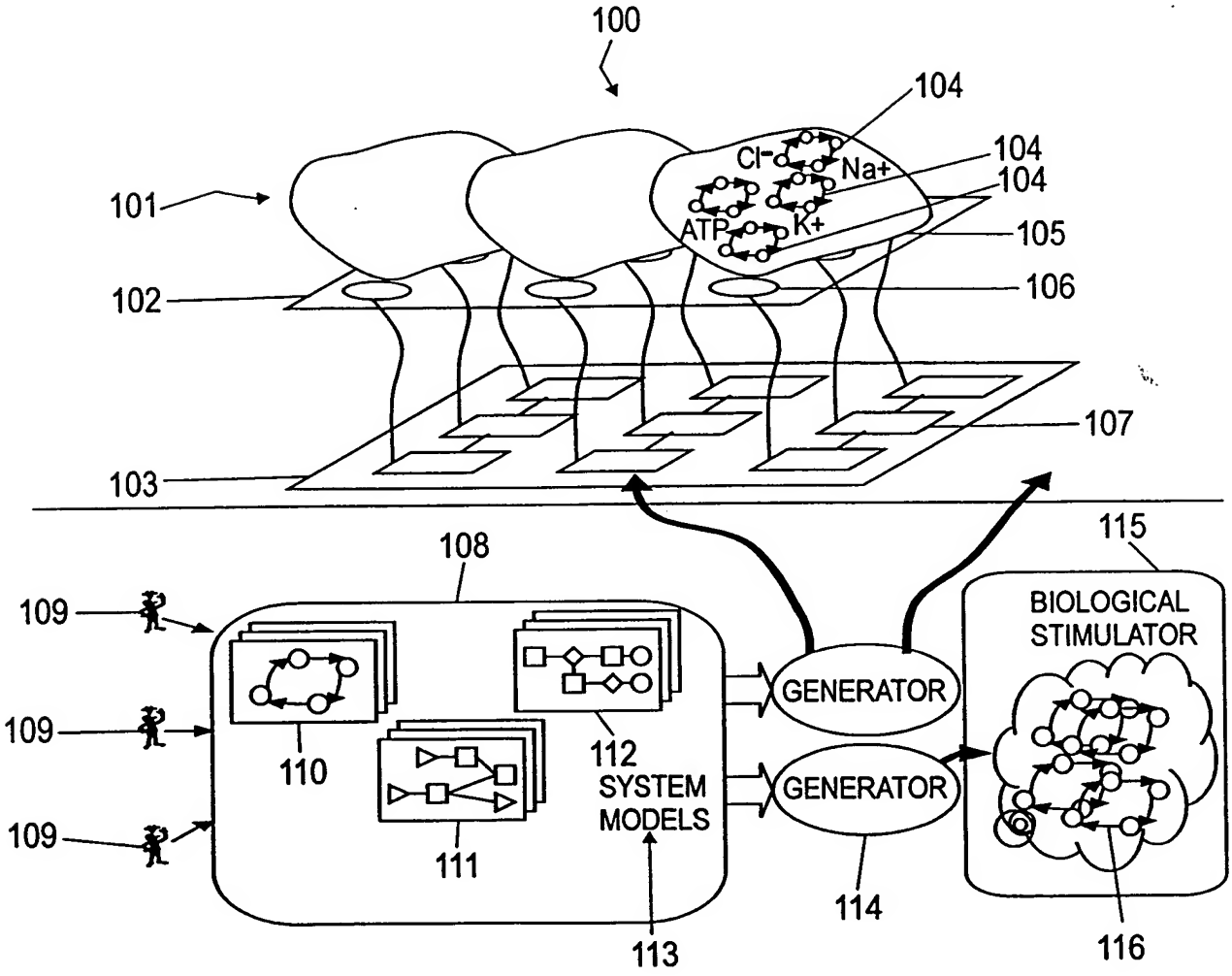

Fig. 1

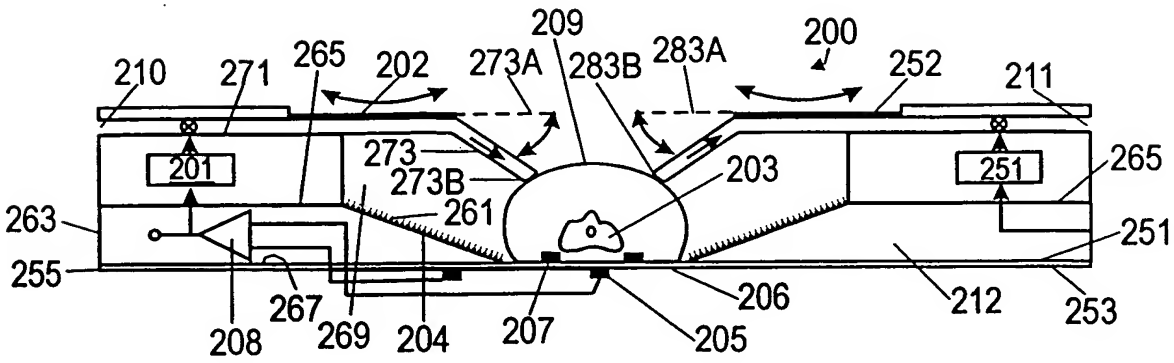
209
210
271
265
202
273A
283B
283A
200
252
211
201
273
273B
203
251
265
263
261
251
255
206
212
253
267
269
204
207
205
208

Fig. 2A

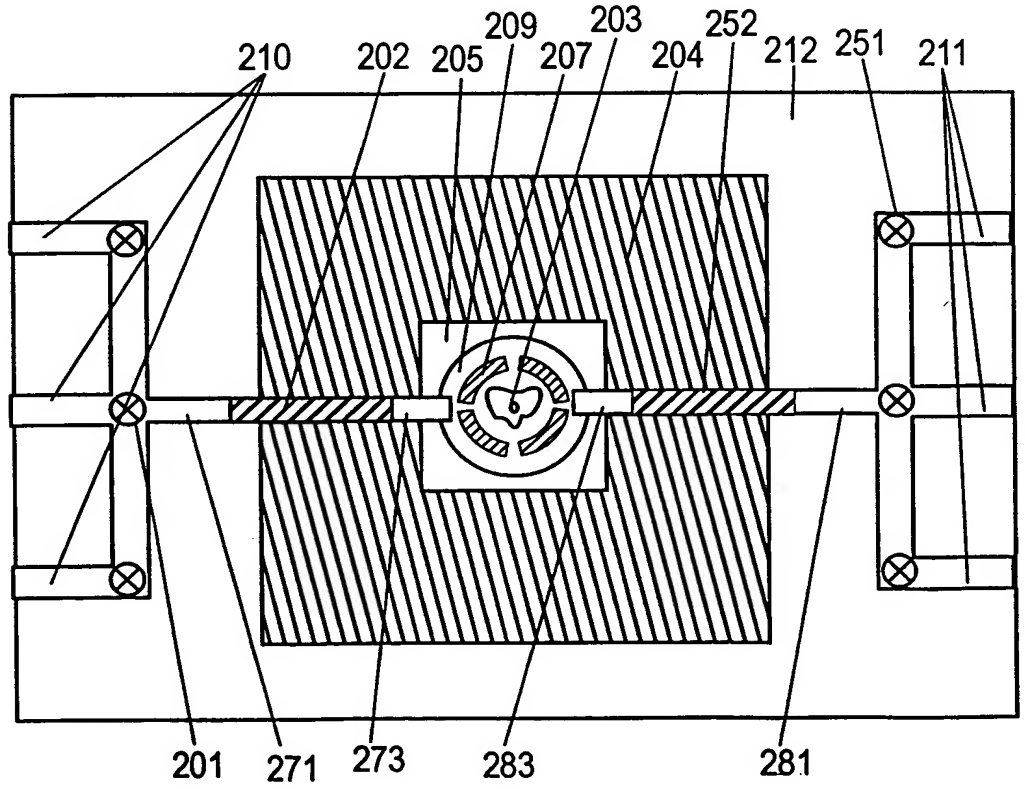
209
203
252
210
202
205
207
204
212
251
211
201
271
273
283
281

Fig. 2B

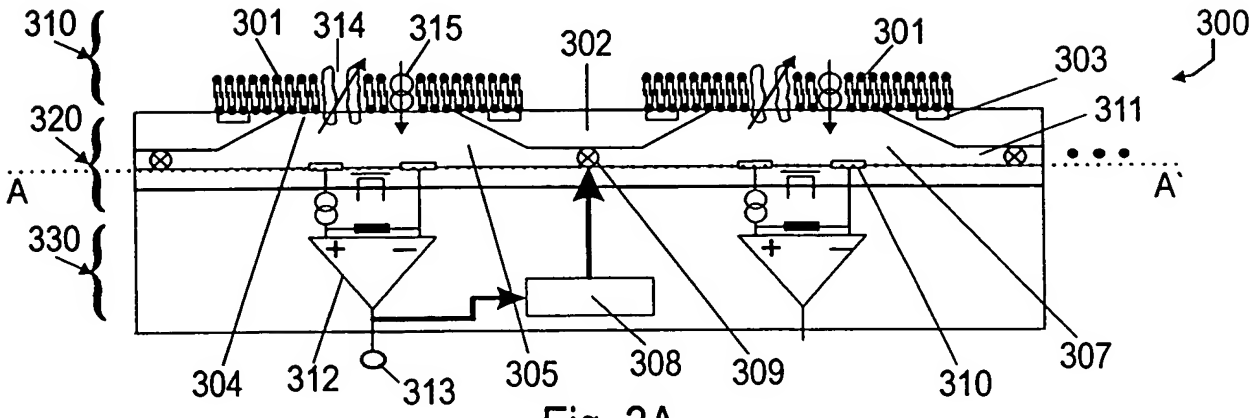

Fig. 3A

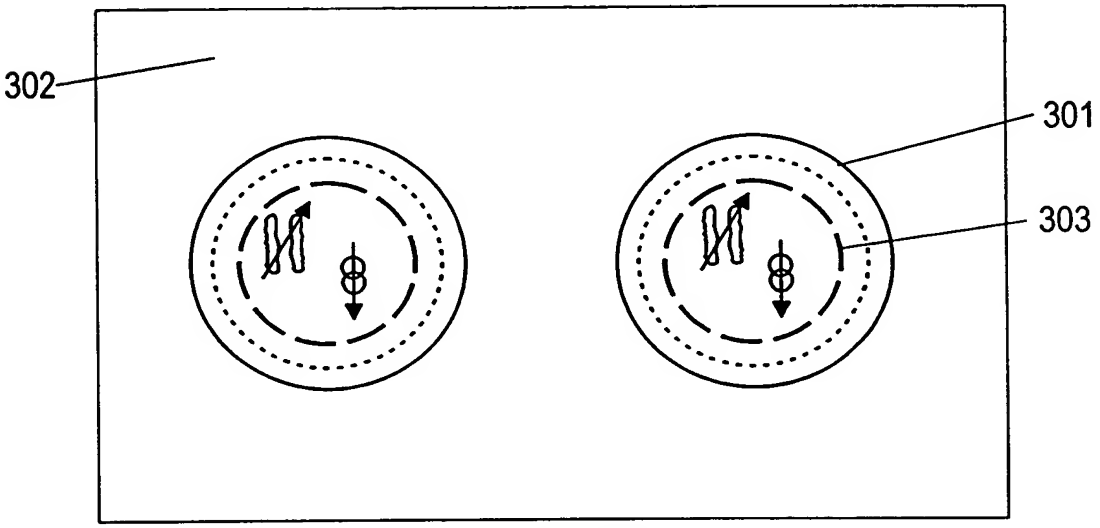

Fig. 3B

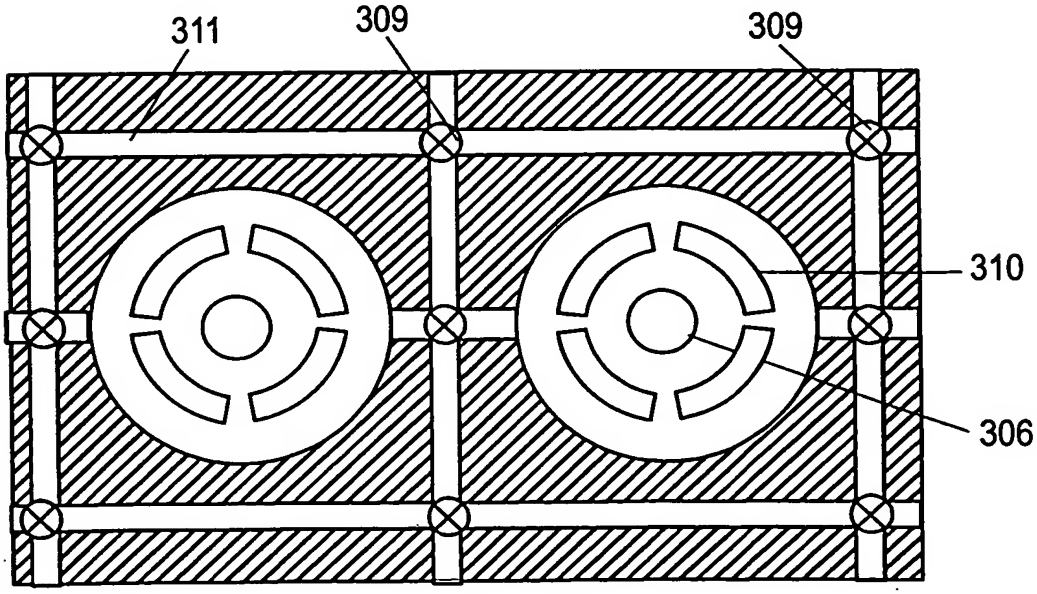

Fig. 3C

10/510500

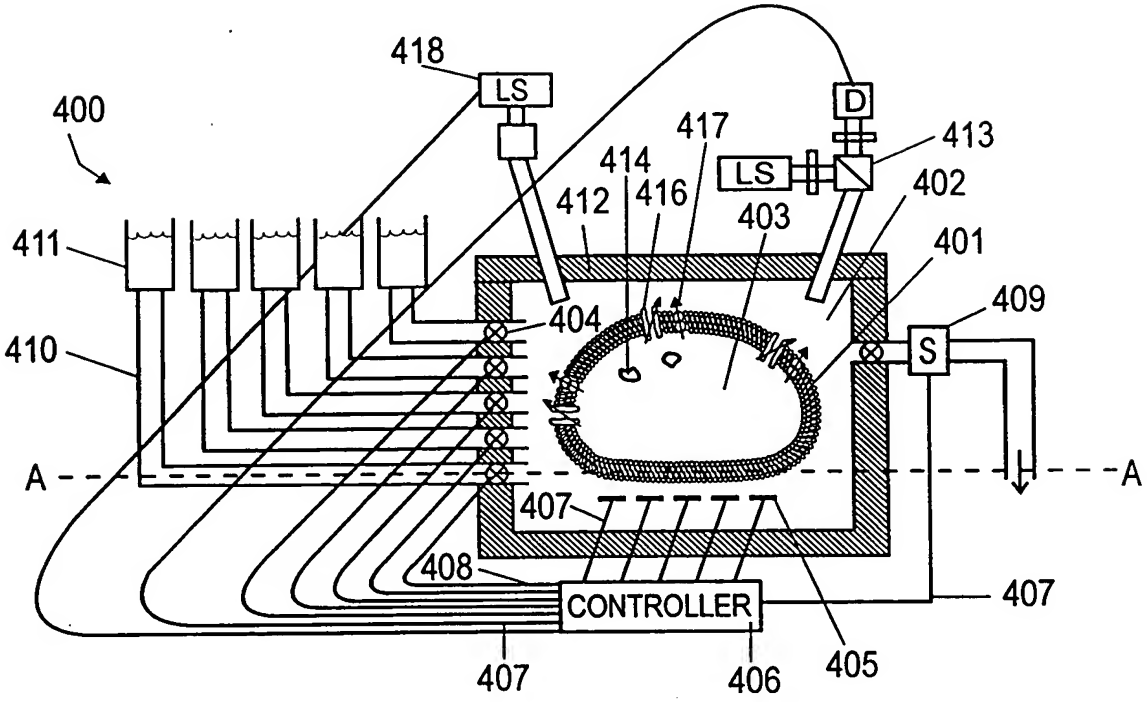

Fig. 4A

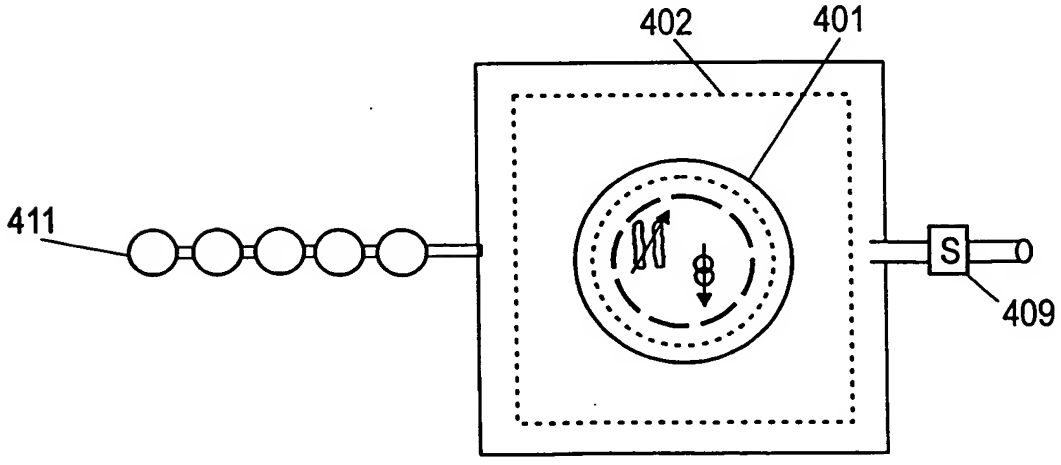

Fig. 4B

10/510500

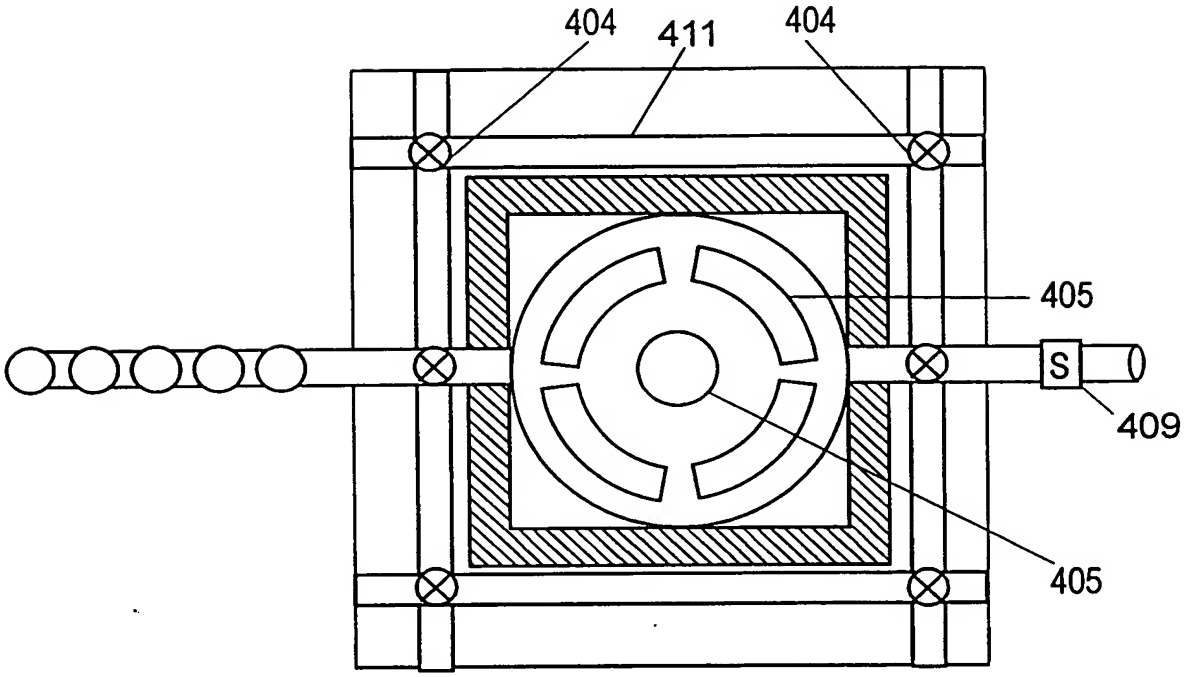

Fig. 4C

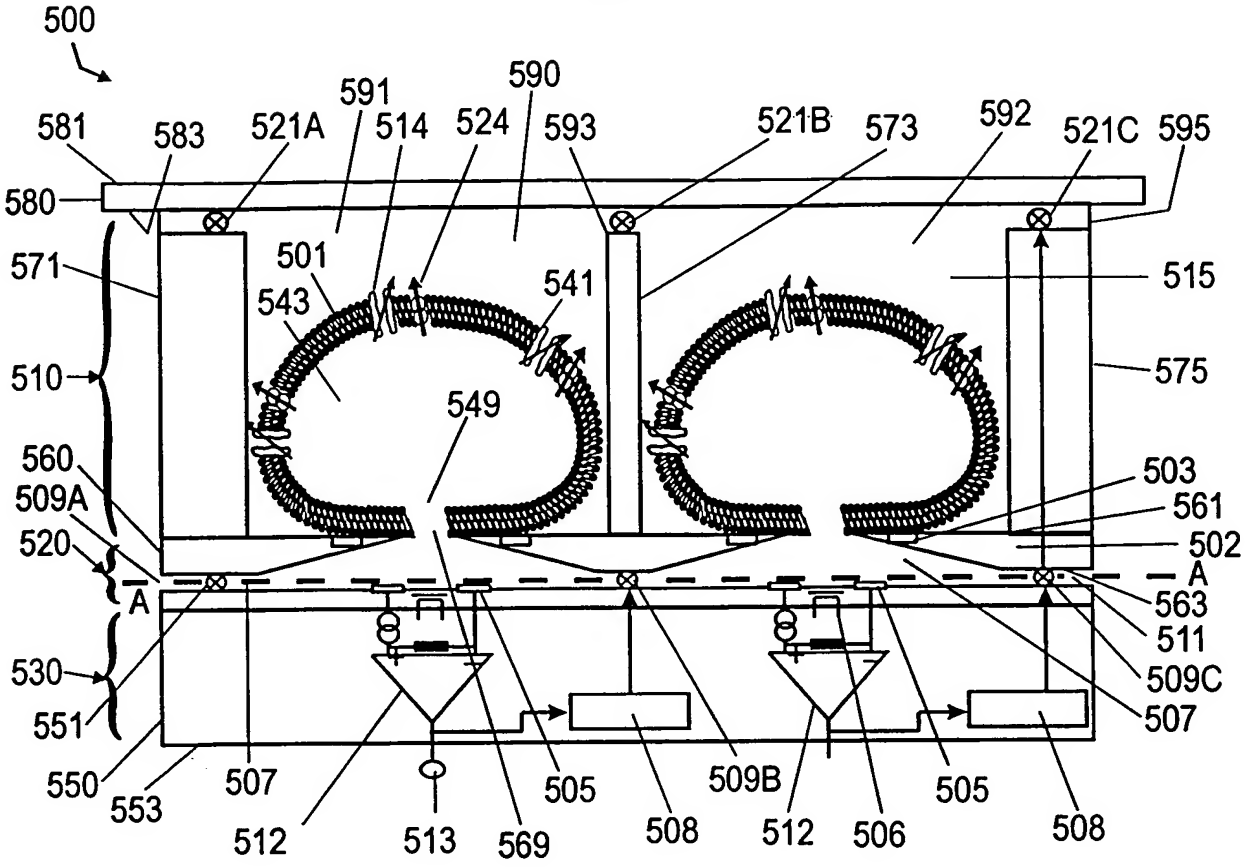
500
581
583
521A
591
514
524
590
593
521B
573
592
521C
595
580
571
501
543
541
515
510
549
575
560
509A
520
503
561
502
A
563
511
509C
530
551
507
550
553
507
512
513
569
505
508
509B
512
506
505
508

Fig. 5A

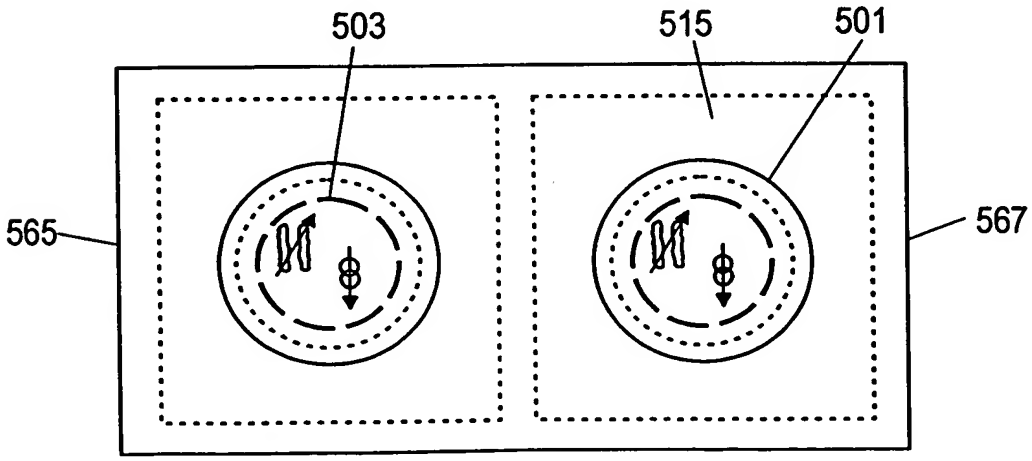
503
515
501
565
567

Fig. 5B

10/510500

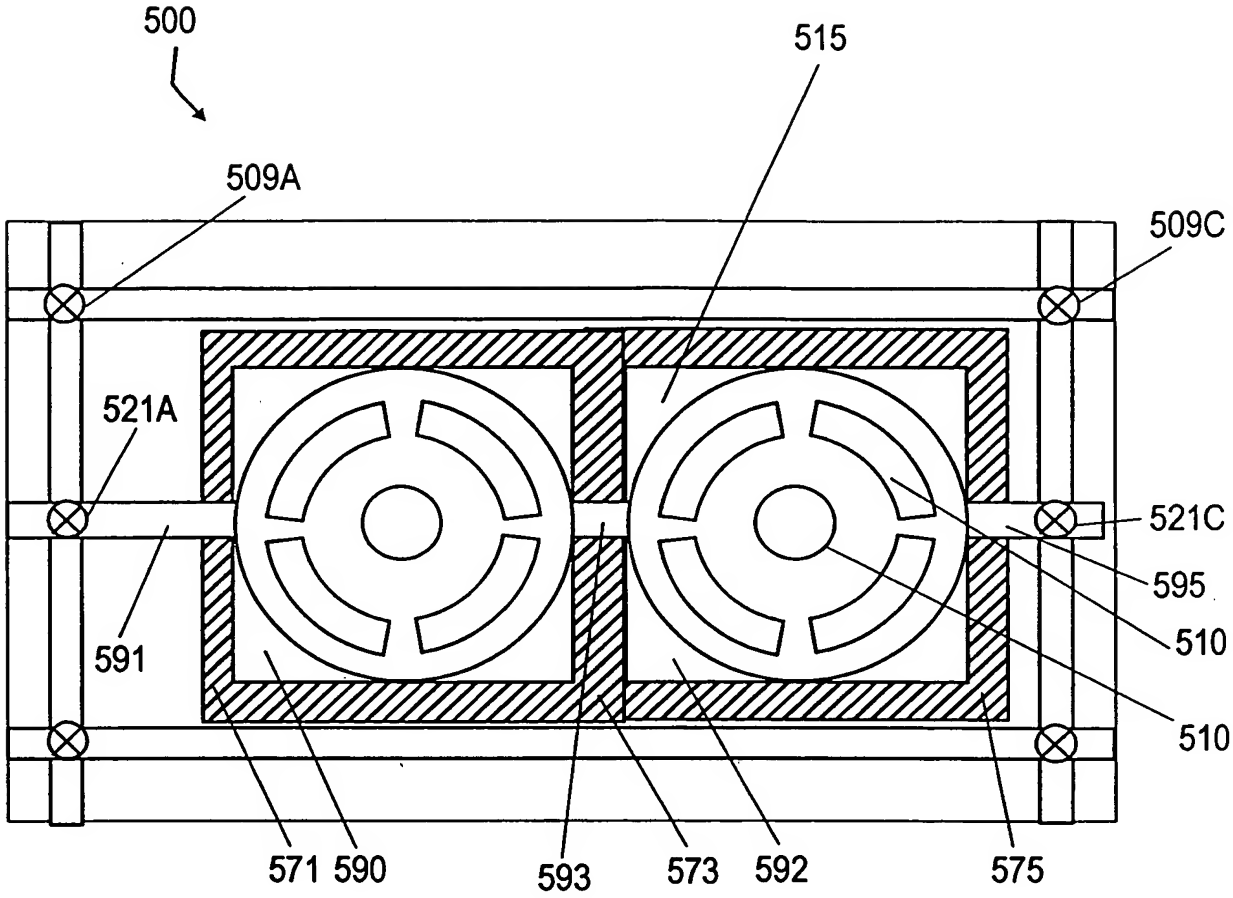

Fig. 5C

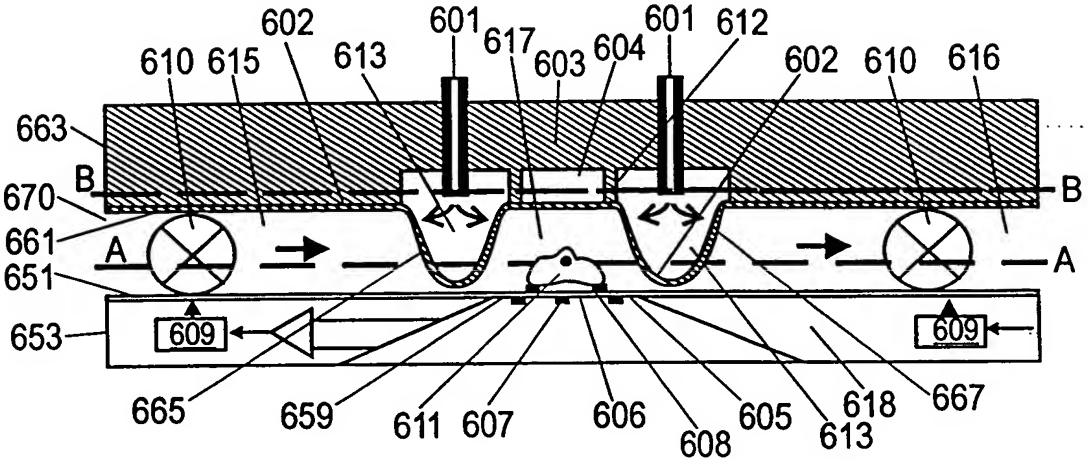
602
601
601
612
610
615
613
617
603
604
602
610
616
663
B
670
661
A
651
653
609
609
665
659
611
607
606
608
605
613
618
667
B
A

Fig. 6A

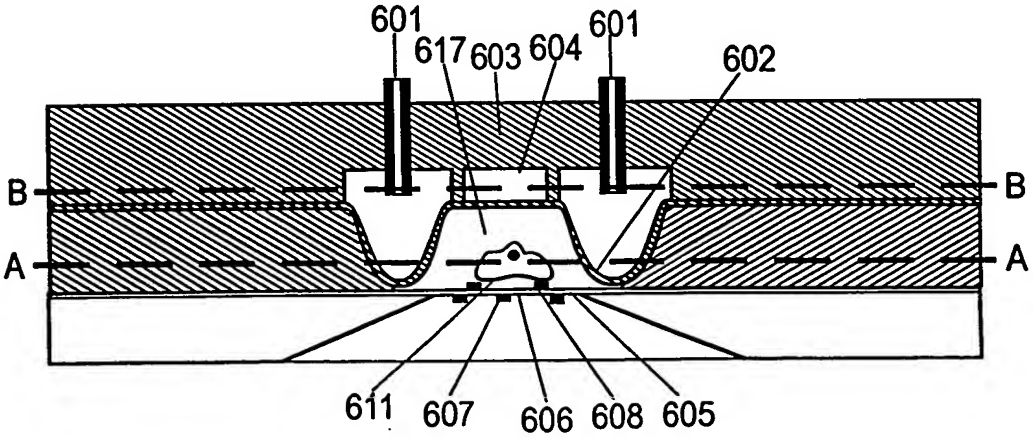
601
617
603
604
601
602
B
A
B
A
611
607
606
608
605

Fig. 6B

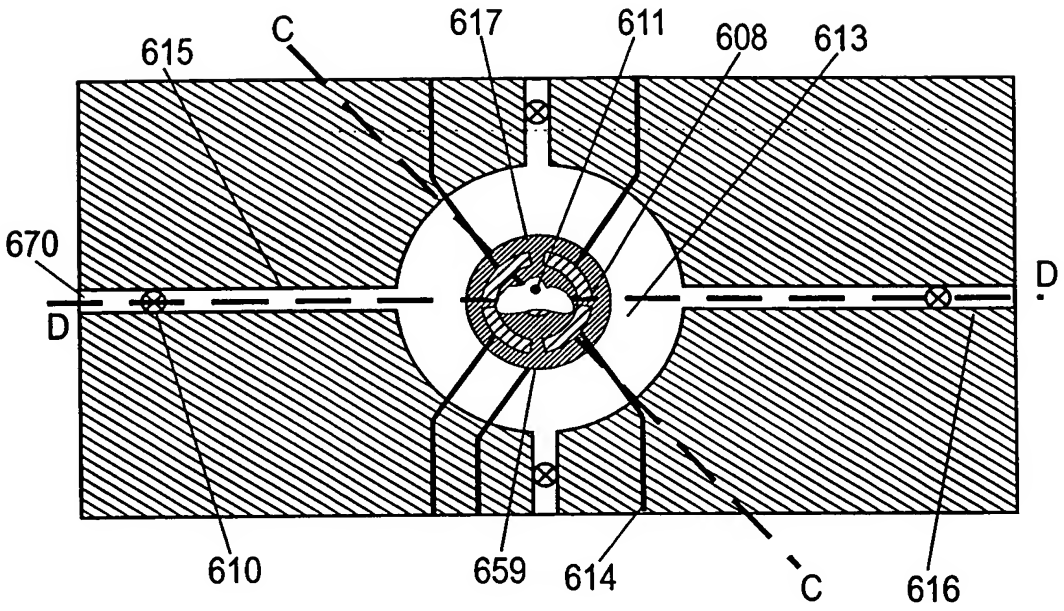

Fig. 6C

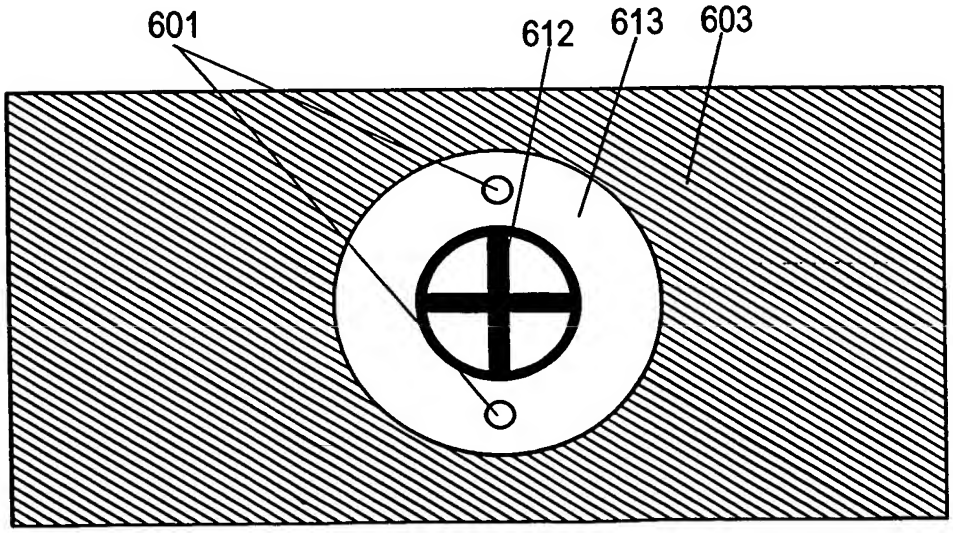

Fig. 6D

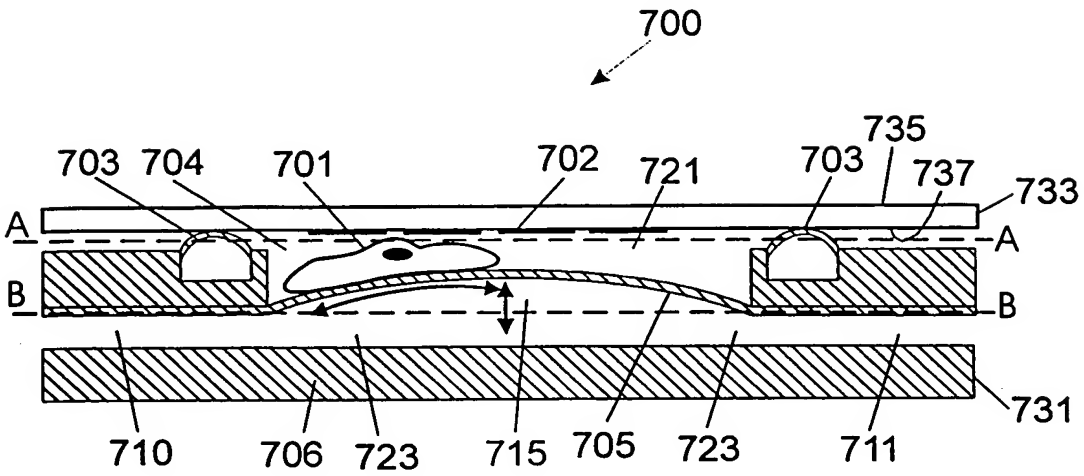
700
735
703
704
701
702
721
703
737
733
A
A
B
B
731
710
706
723
715
705
723
711

Fig. 7A

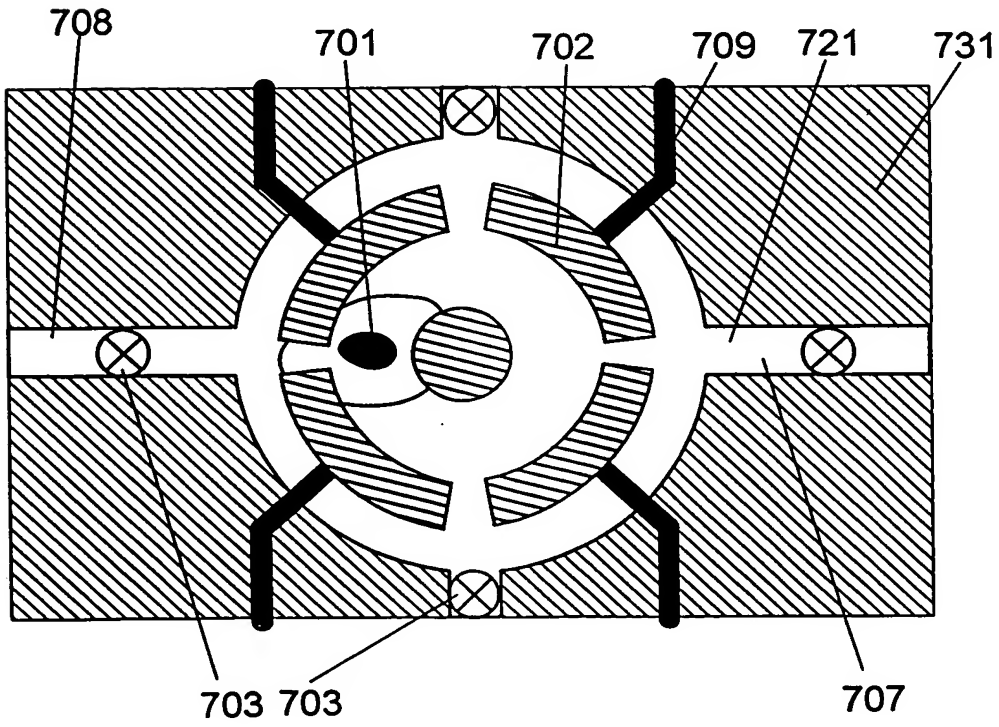
708
701
702
709
721
731
703
703
707

Fig. 7B

10/510500

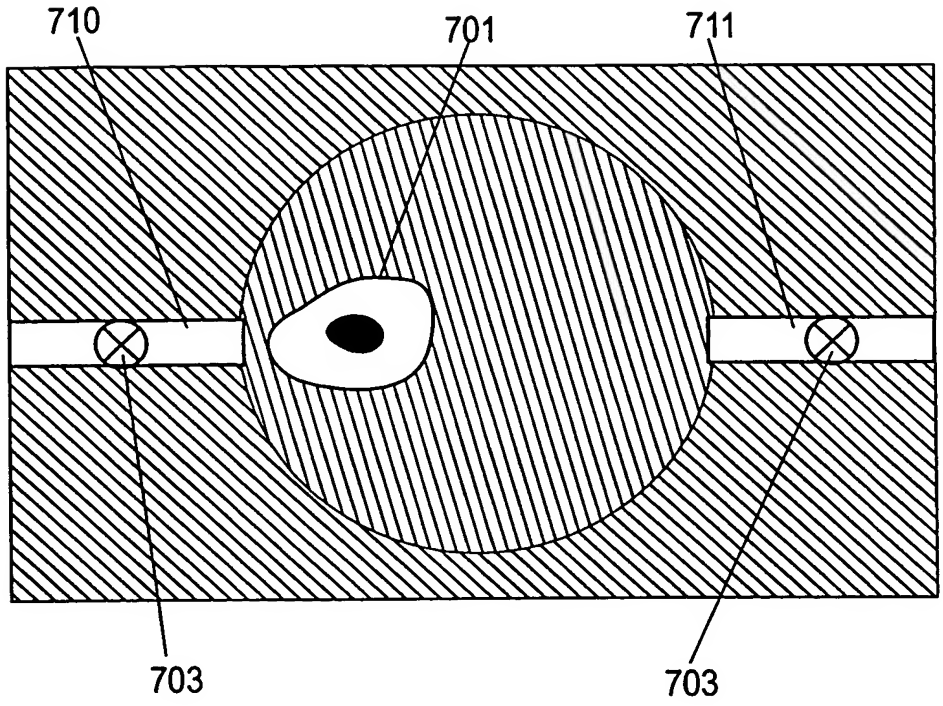

Fig. 7C

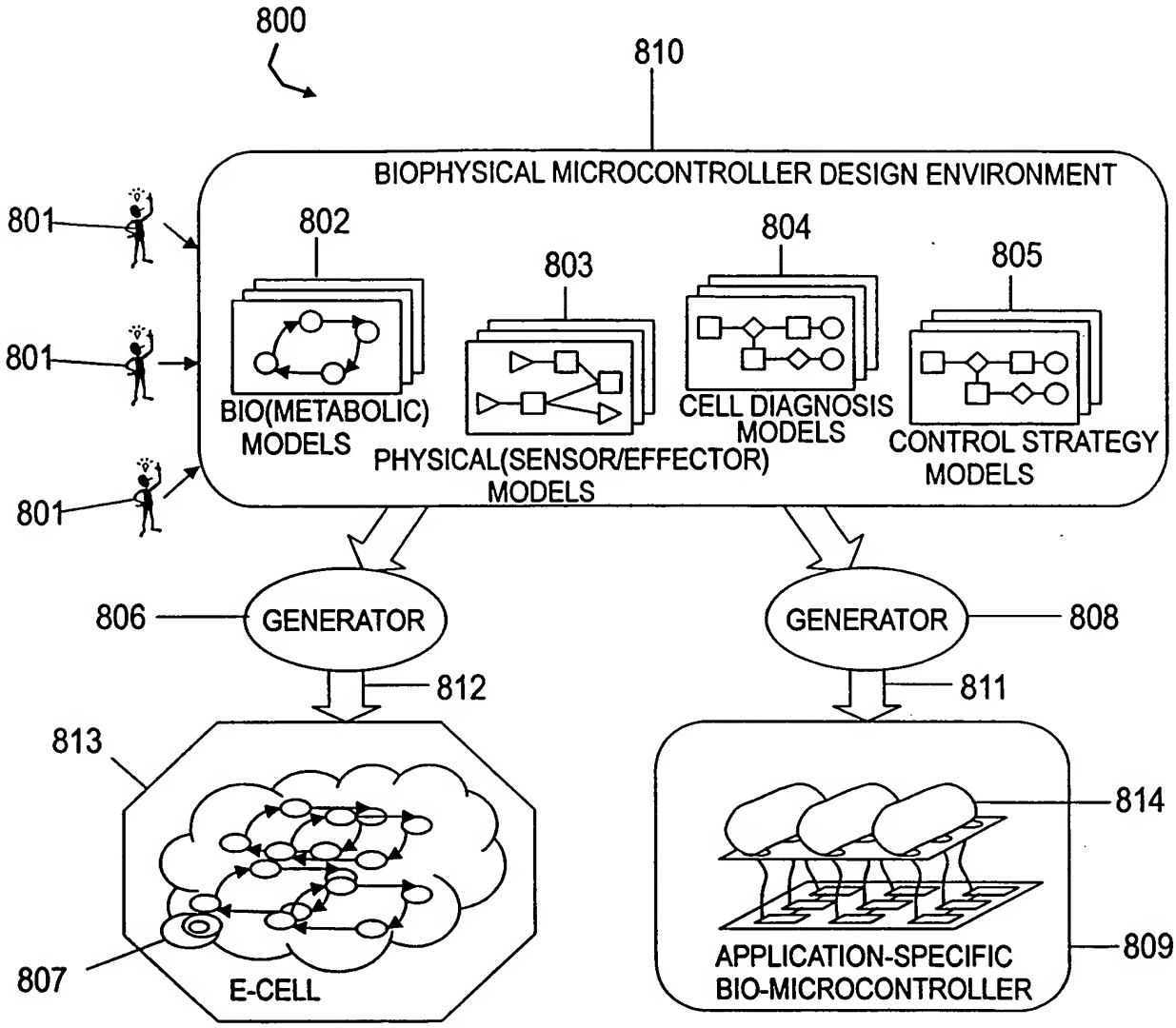
800
810
BIOPHYSICAL MICROCONTROLLER DESIGN ENVIRONMENT
801
801
801
802
803
804
805
BIO(METABOLIC) MODELS
PHYSICAL(SENSOR/EFFECTOR) MODELS
CELL DIAGNOSIS MODELS
CONTROL STRATEGY MODELS
806
GENERATOR
GENERATOR
808
812
811
813
814
807
E-CELL
APPLICATION-SPECIFIC BIO-MICROCONTROLLER
809

Fig. 8

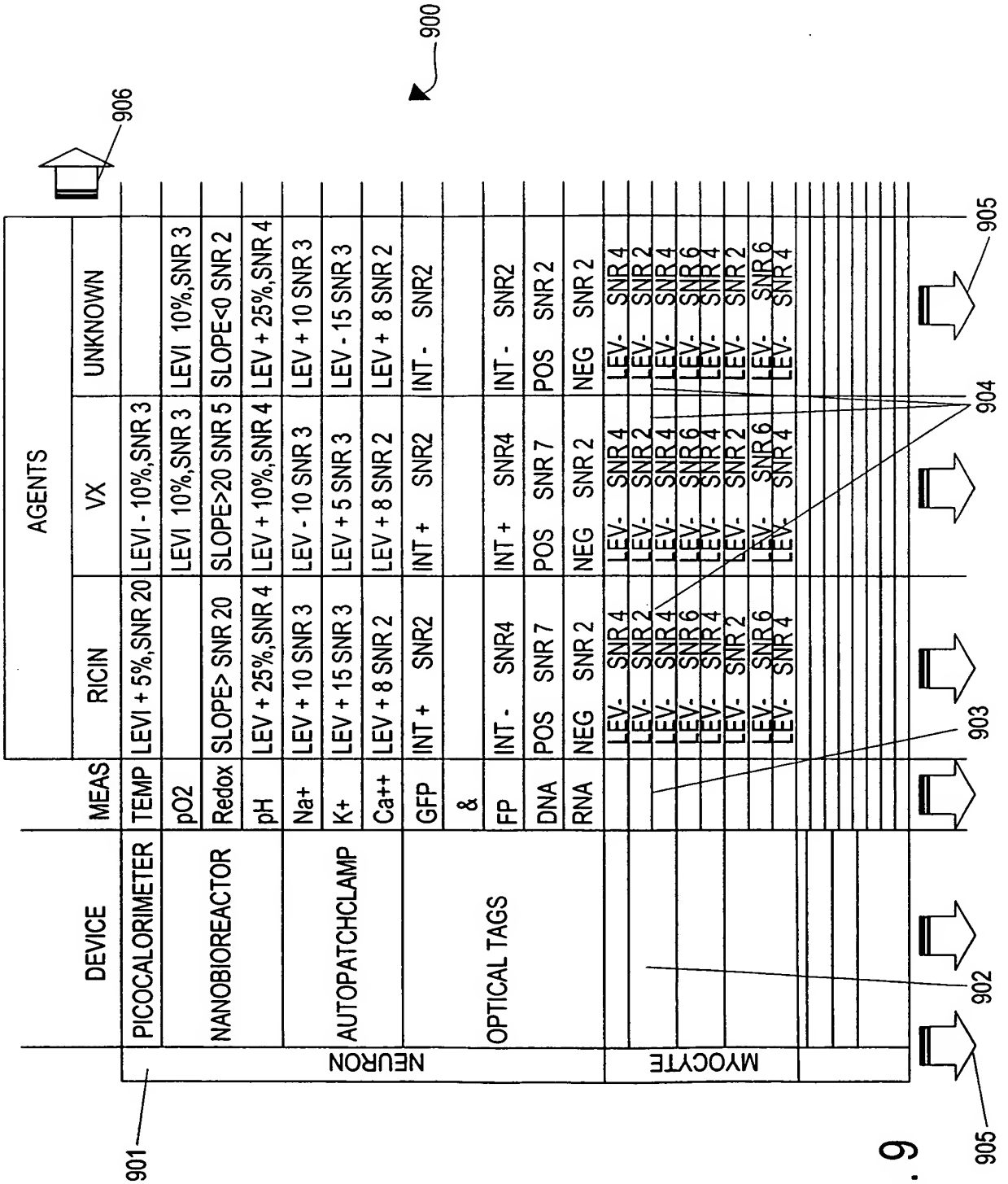
900
906
AGENTS
RICIN
VX
UNKNOWN
DEVICE
MEAS
PICOCALORIMETER
TEMP
LEVI + 5%,SNR 20
LEVI - 10%,SNR 3
NANOBIOREACTOR
pO2
LEVI 10%,SNR 3
LEVI 10%,SNR 3
Redox
SLOPE> SNR 20
SLOPE>20 SNR 5
SLOPE<0 SNR 2
pH
LEV + 25%,SNR 4
LEV + 10%,SNR 4
LEV + 25%,SNR 4
AUTOPATCHCLAMP
Na+
LEV + 10 SNR 3
LEV - 10 SNR 3
LEV + 10 SNR 3
K+
LEV + 15 SNR 3
LEV + 5 SNR 3
LEV - 15 SNR 3
Ca++
LEV + 8 SNR 2
LEV + 8 SNR 2
LEV + 8 SNR 2
OPTICAL TAGS
GFP & FP
INT + SNR2
INT + SNR2
INT - SNR2
INT - SNR4
INT + SNR4
INT - SNR2
DNA
POS SNR 7
POS SNR 7
POS SNR 2
RNA
NEG SNR 2
NEG SNR 2
NEG SNR 2
NEURON
MYOCYTE
LEV- SNR 4
LEV- SNR 2
LEV- SNR 4
LEV- SNR 6
LEV- SNR 4
LEV- SNR 2
LEV- SNR 6
LEV- SNR 4
901
902
903
904
905
905

Fig. 9

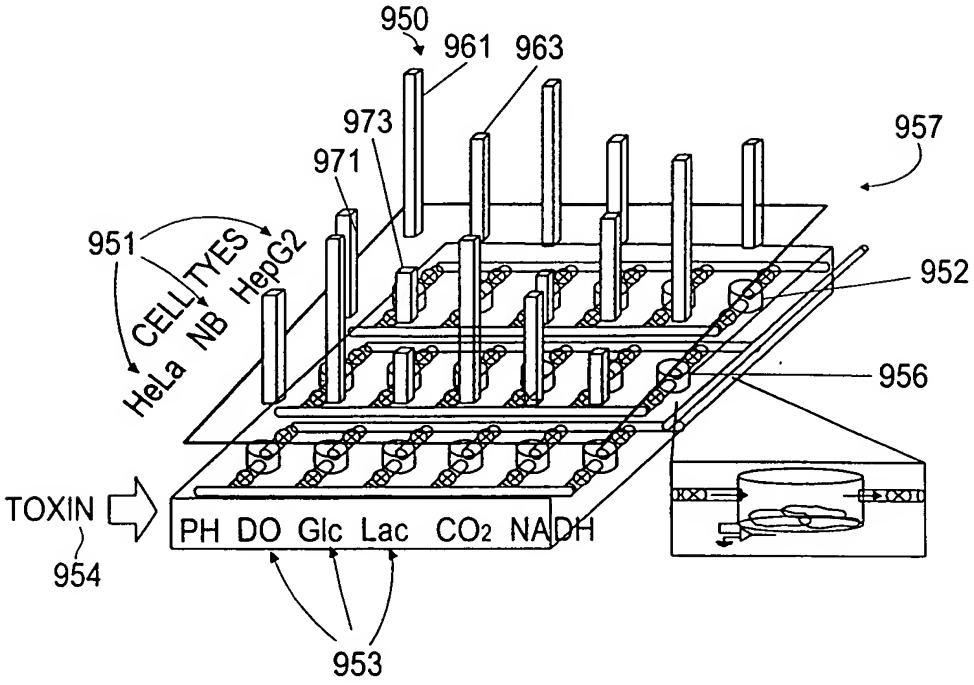
950
961
963
973
971
957
951
CELL TYES
HeLa
NB
HepG2
952
956
TOXIN
954
PH DO Glc Lac CO2 NADH
953

Fig. 9A

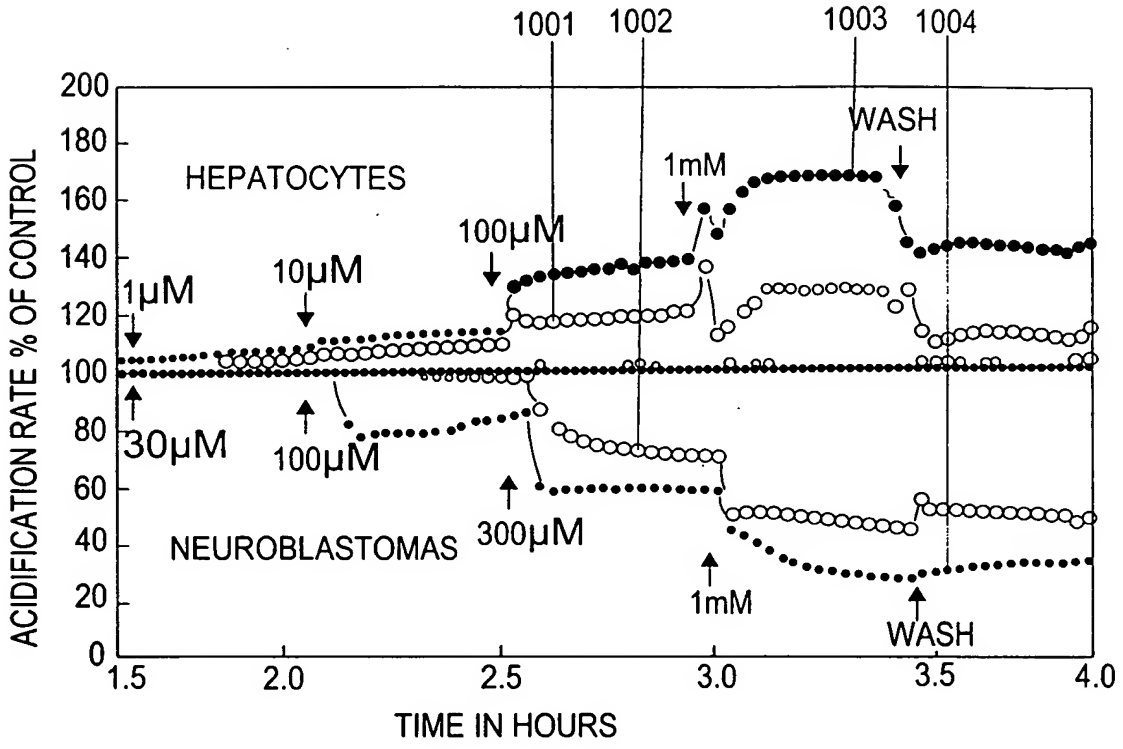
1001
1002
1003
1004
WASH
HEPATOCYTES
1mM
100μM
10μM
1μM
30μM
100μM
300μM
NEUROBLASTOMAS
1mM
WASH
ACIDIFICATION RATE % OF CONTROL
200
180
160
140
120
100
80
60
40
20
0
1.5
2.0
2.5
3.0
3.5
4.0
TIME IN HOURS

Fig. 10

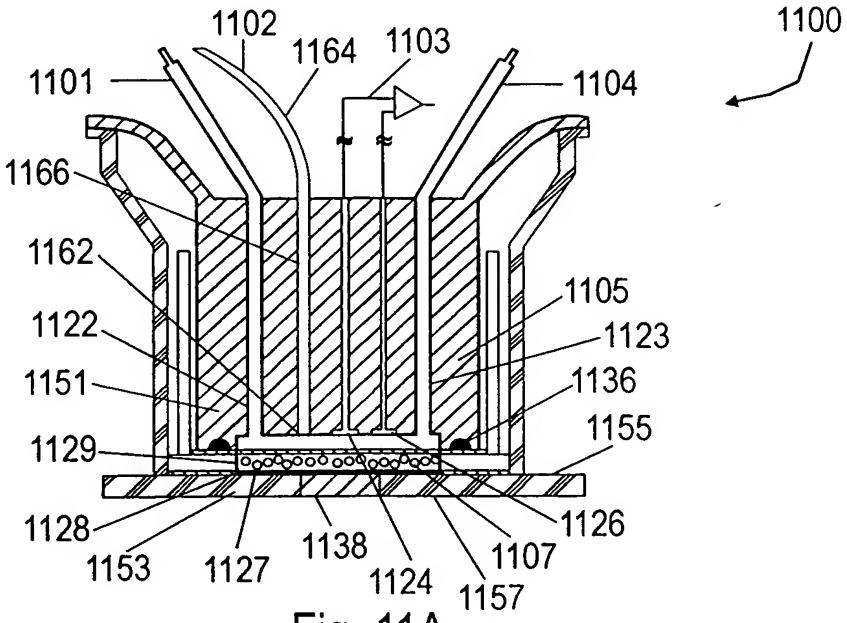

Fig. 11A

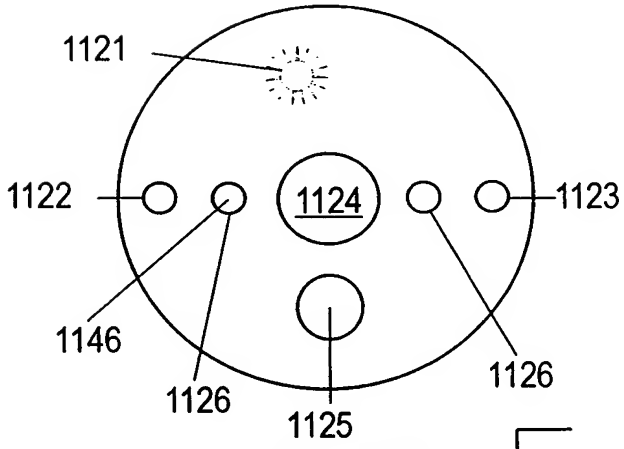

Fig. 11B

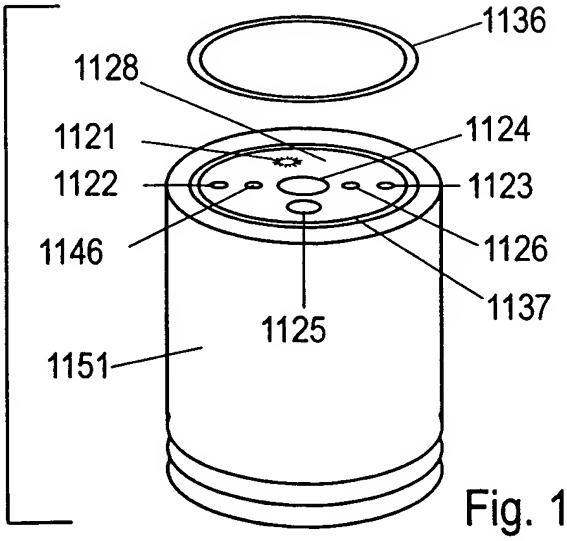

Fig. 11C

10/510500

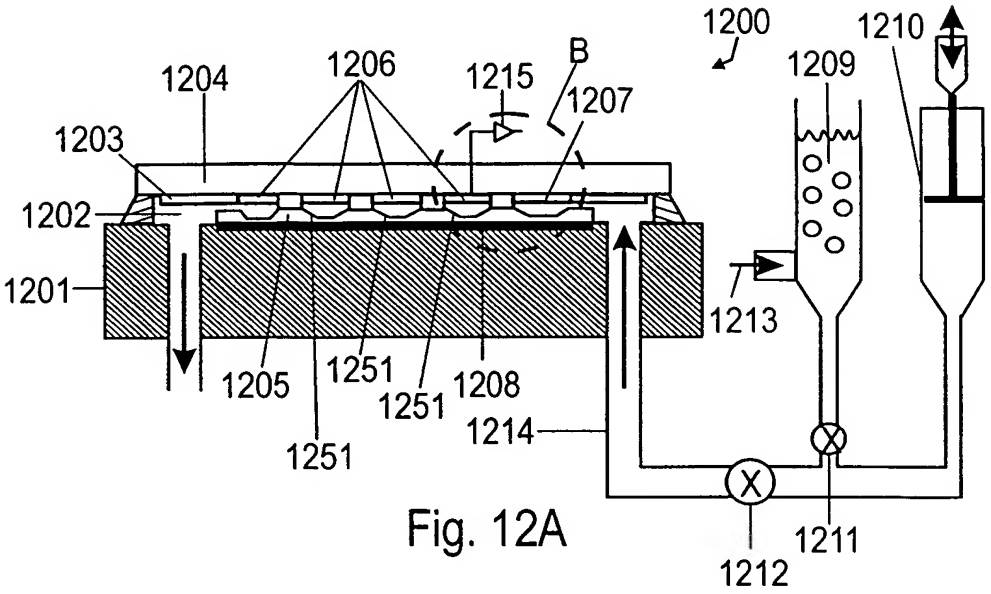

Fig. 12A

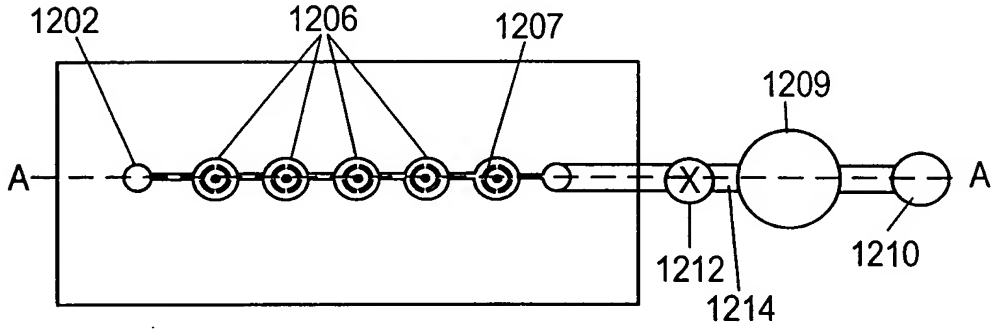

Fig. 12B

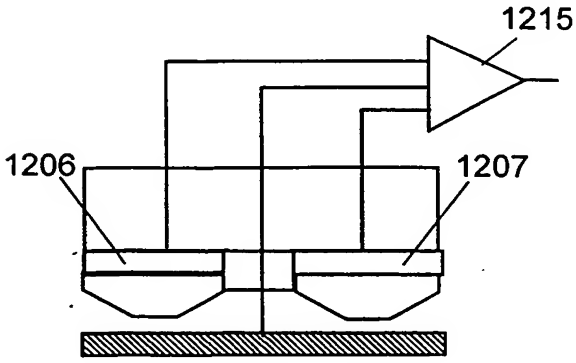

Fig. 12C

10/510500

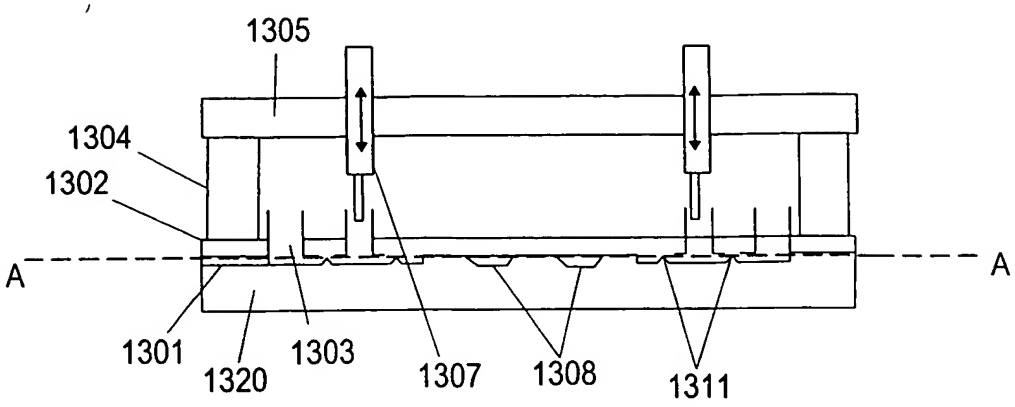

FIG.13A

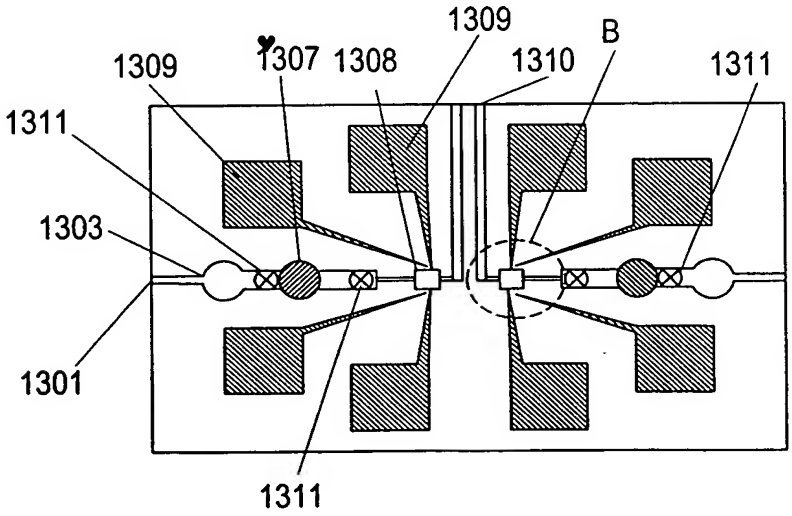

FIG.13B

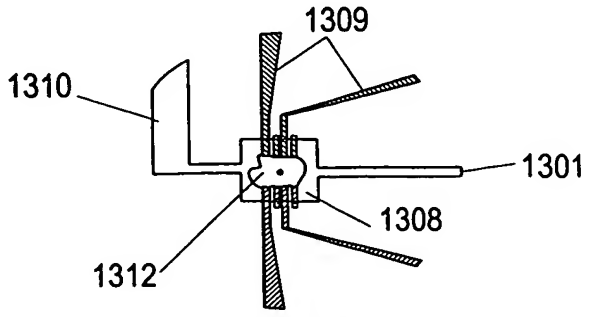

FIG.13C

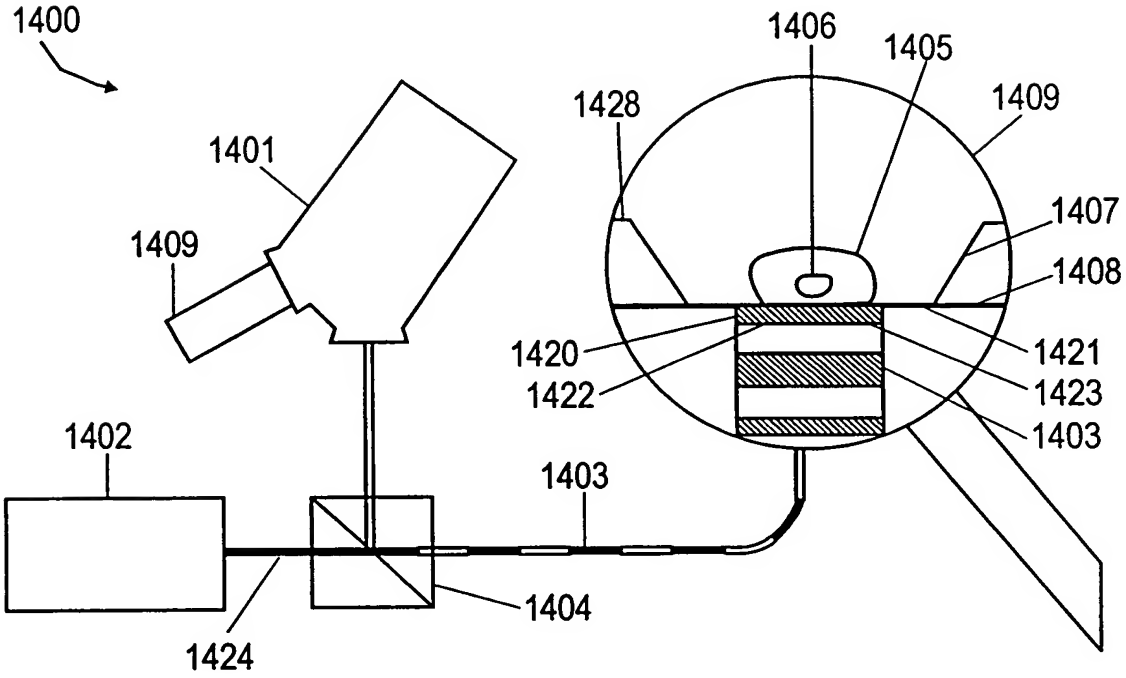
1400
1406
1405
1428
1409
1401
1407
1409
1408
1420
1421
1422
1423
1403
1402
1403
1404
1424

Fig. 14

10/510501

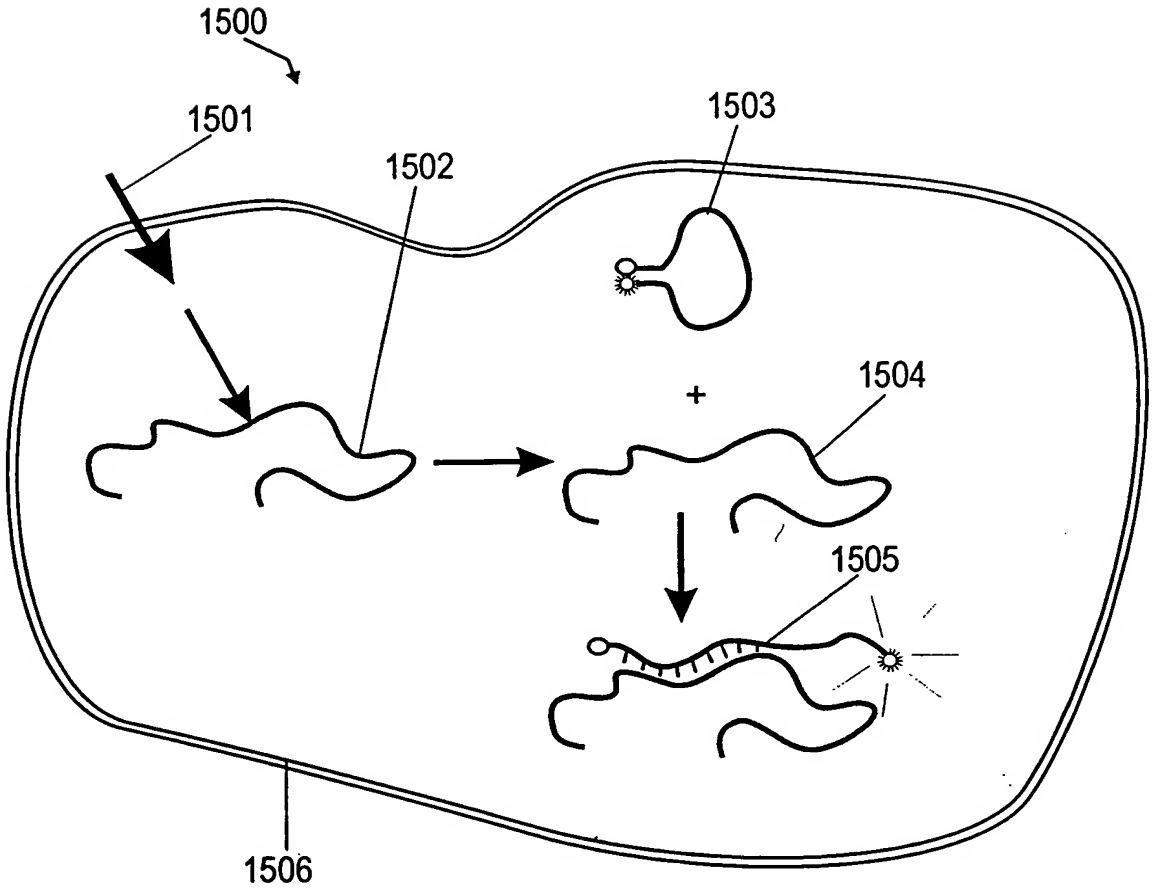

Fig. 15

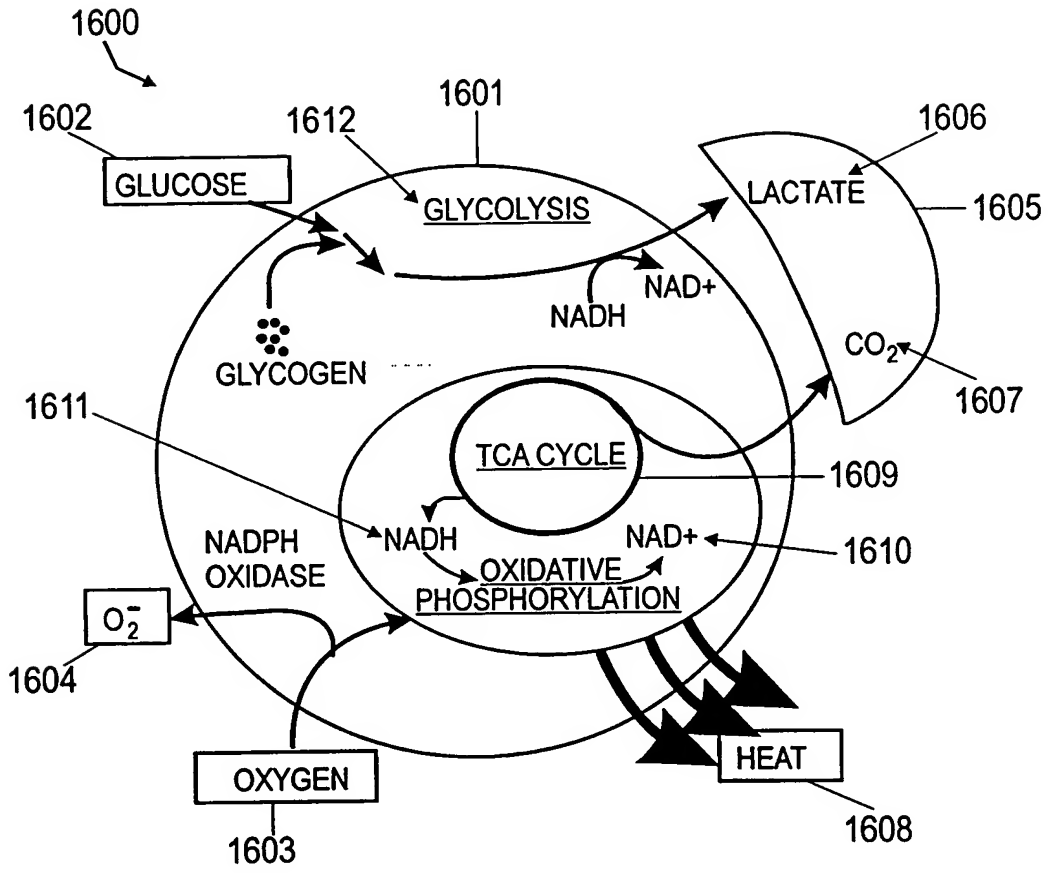
1600
1602
1612
1601
1606
GLUCOSE
GLYCOLYSIS
LACTATE
1605
NAD+
NADH
GLYCOGEN
CO_2
1607
1611
TCA CYCLE
1609
NADH
NAD+
1610
NADPH
OXIDASE
OXIDATIVE
PHOSPHORYLATION
O_2^-
1604
HEAT
OXYGEN
1608
1603

Fig. 16

10/510500

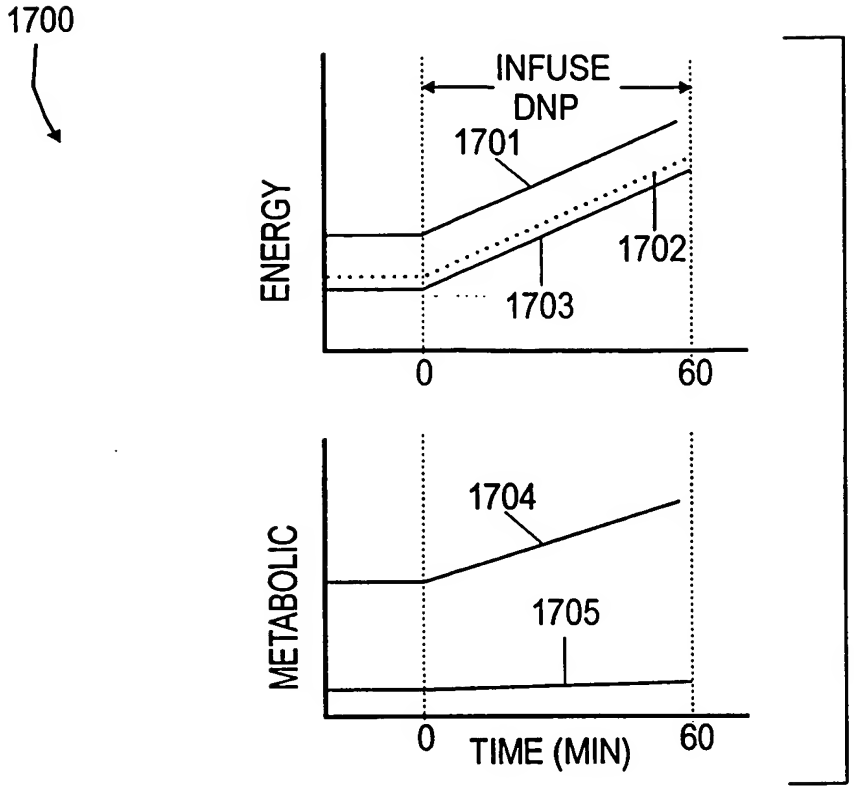

Fig. 17A

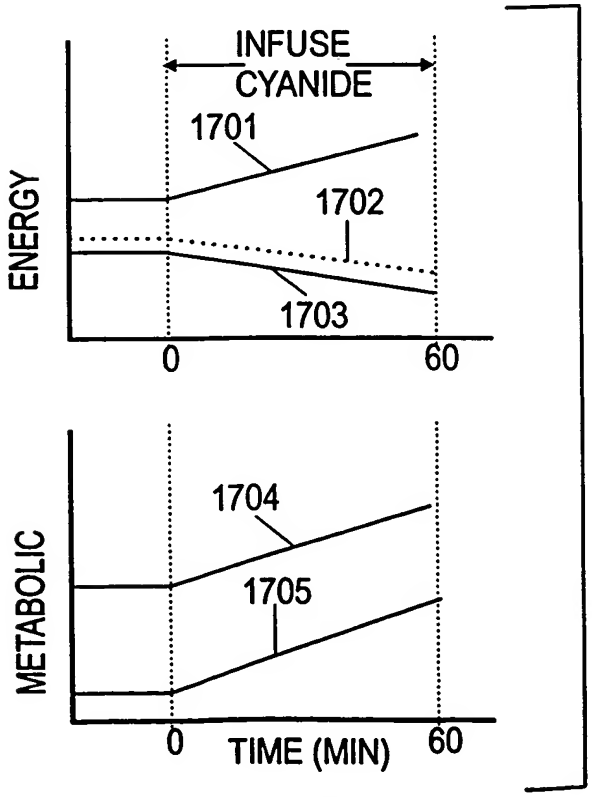

Fig. 17B

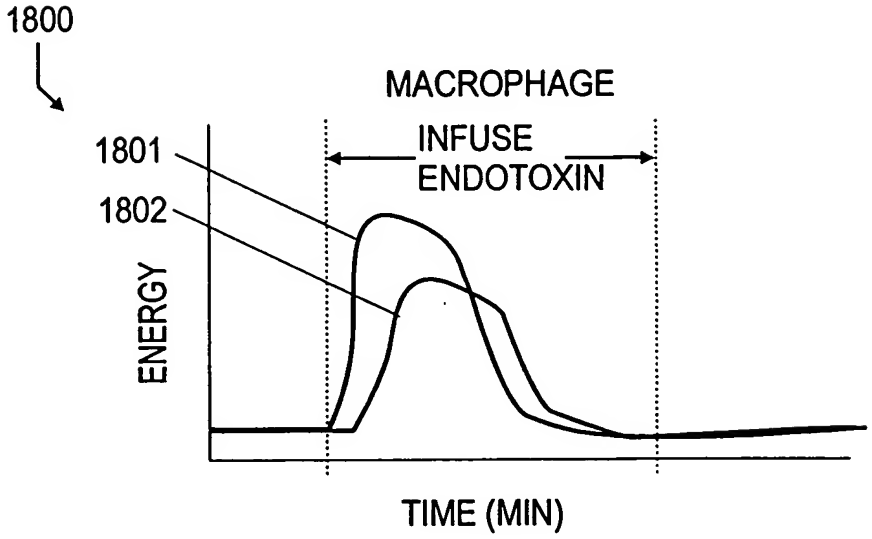

Fig. 18A

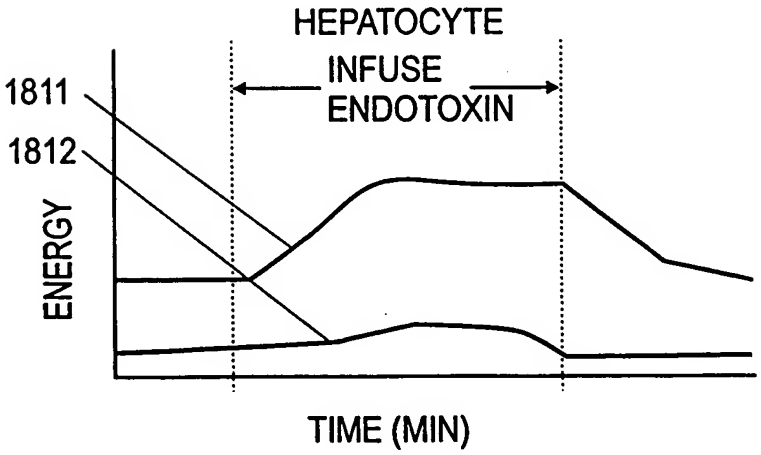

Fig. 18B

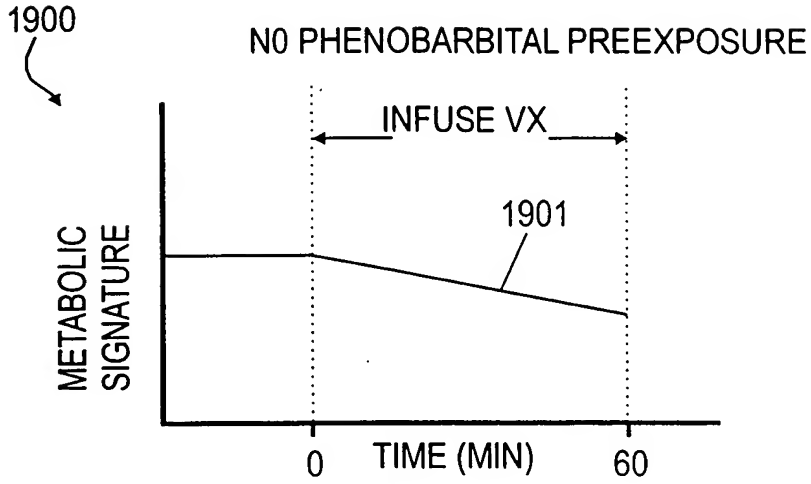

Fig. 19A

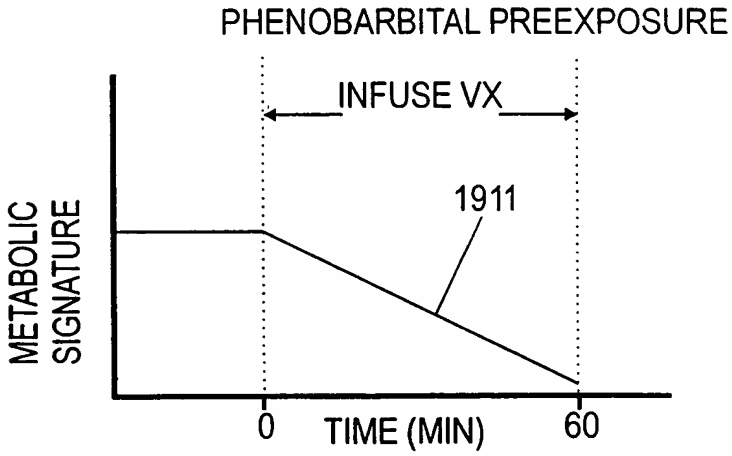

Fig. 19B

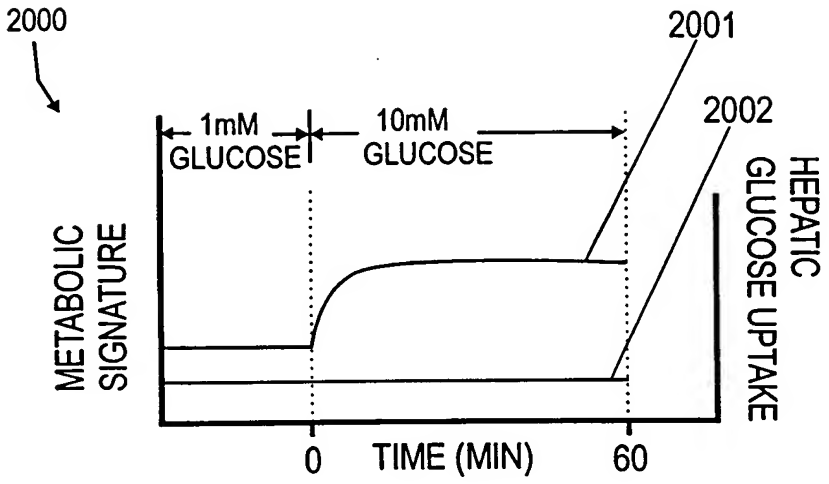
2000
2001
2002
1mM GLUCOSE
10mM GLUCOSE
METABOLIC SIGNATURE
HEPATIC GLUCOSE UPTAKE
0
TIME (MIN)
60

Fig. 20

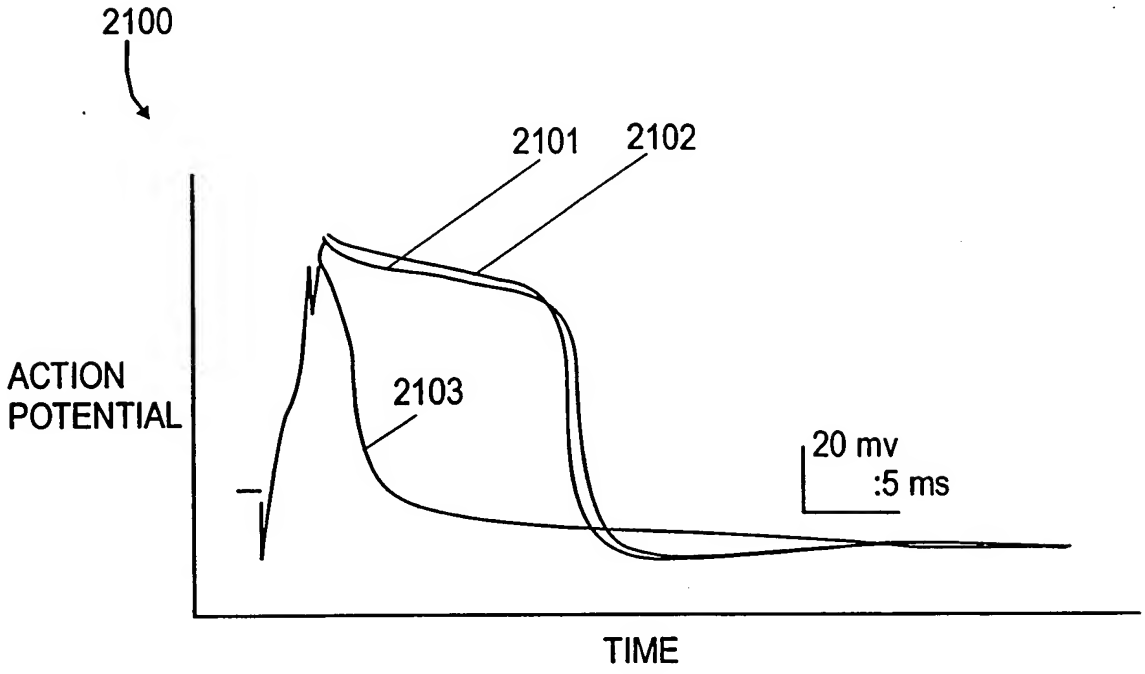

Fig. 21

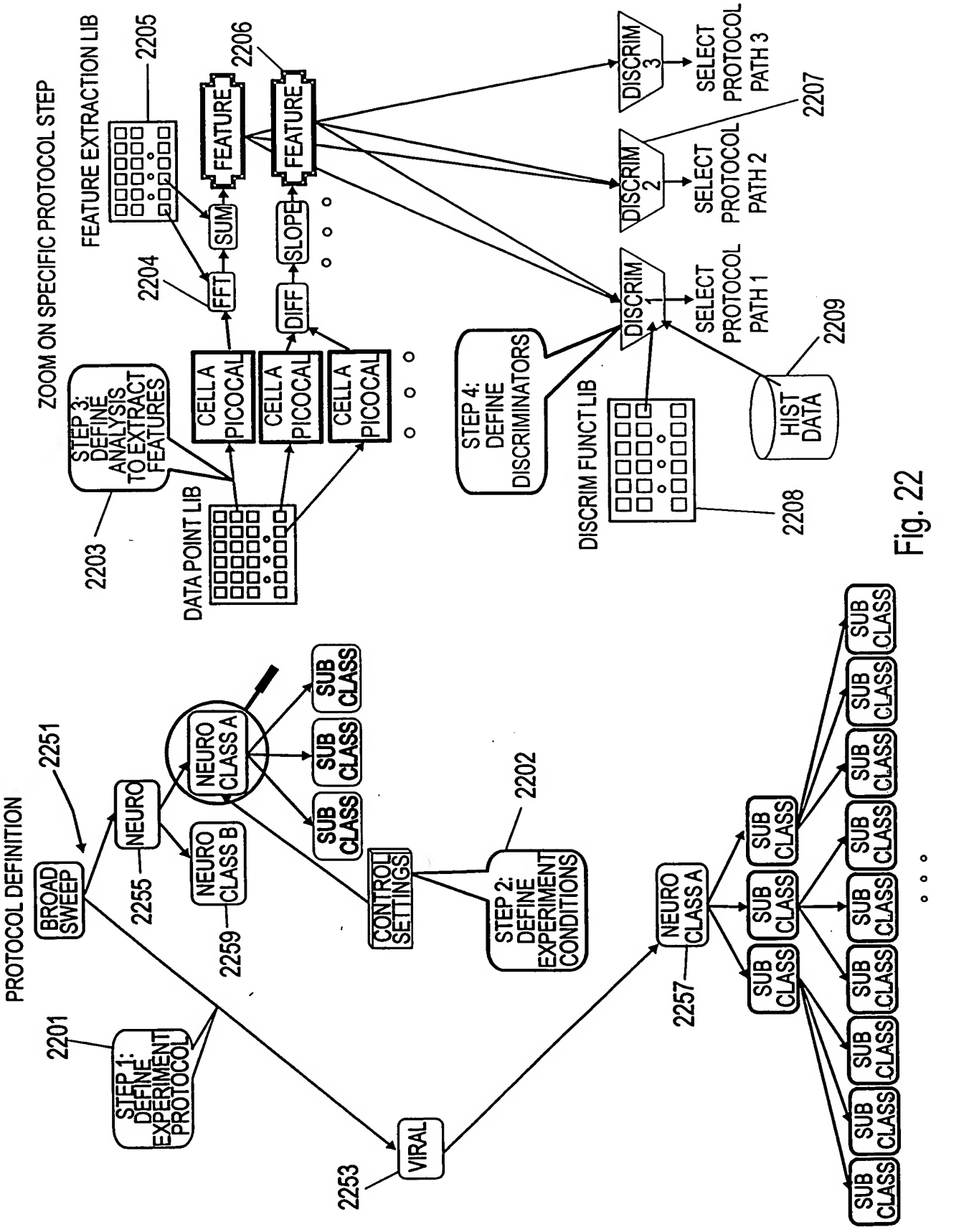
PROTOCOL DEFINITION
2251
BROAD SWEEP
NEURO
NEURO CLASS A
NEURO CLASS B
SUB CLASS
SUB CLASS
SUB CLASS
2255
2259
CONTROL SETTINGS
2202
STEP 2: DEFINE EXPERIMENT CONDITIONS
2201
STEP 1: DEFINE EXPERIMENT PROTOCOL
VIRAL
2253
NEURO CLASS A
2257
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
SUB CLASS
ZOOM ON SPECIFIC PROTOCOL STEP
FEATURE EXTRACTION LIB
2205
2206
FEATURE
FEATURE
SUM
SLOPE
2204
FFT
DIFF
STEP 3: DEFINE ANALYSIS TO EXTRACT FEATURES
2203
CELL A PICOCAL
CELL A PICOCAL
CELL A PICOCAL
DATA POINT LIB
STEP 4: DEFINE DISCRIMINATORS
DISCRIM FUNCT LIB
DISCRIM 1
DISCRIM 2
DISCRIM 3
SELECT PROTOCOL PATH 1
SELECT PROTOCOL PATH 2
SELECT PROTOCOL PATH 3
2207
HIST DATA
2209
2208

Fig. 22

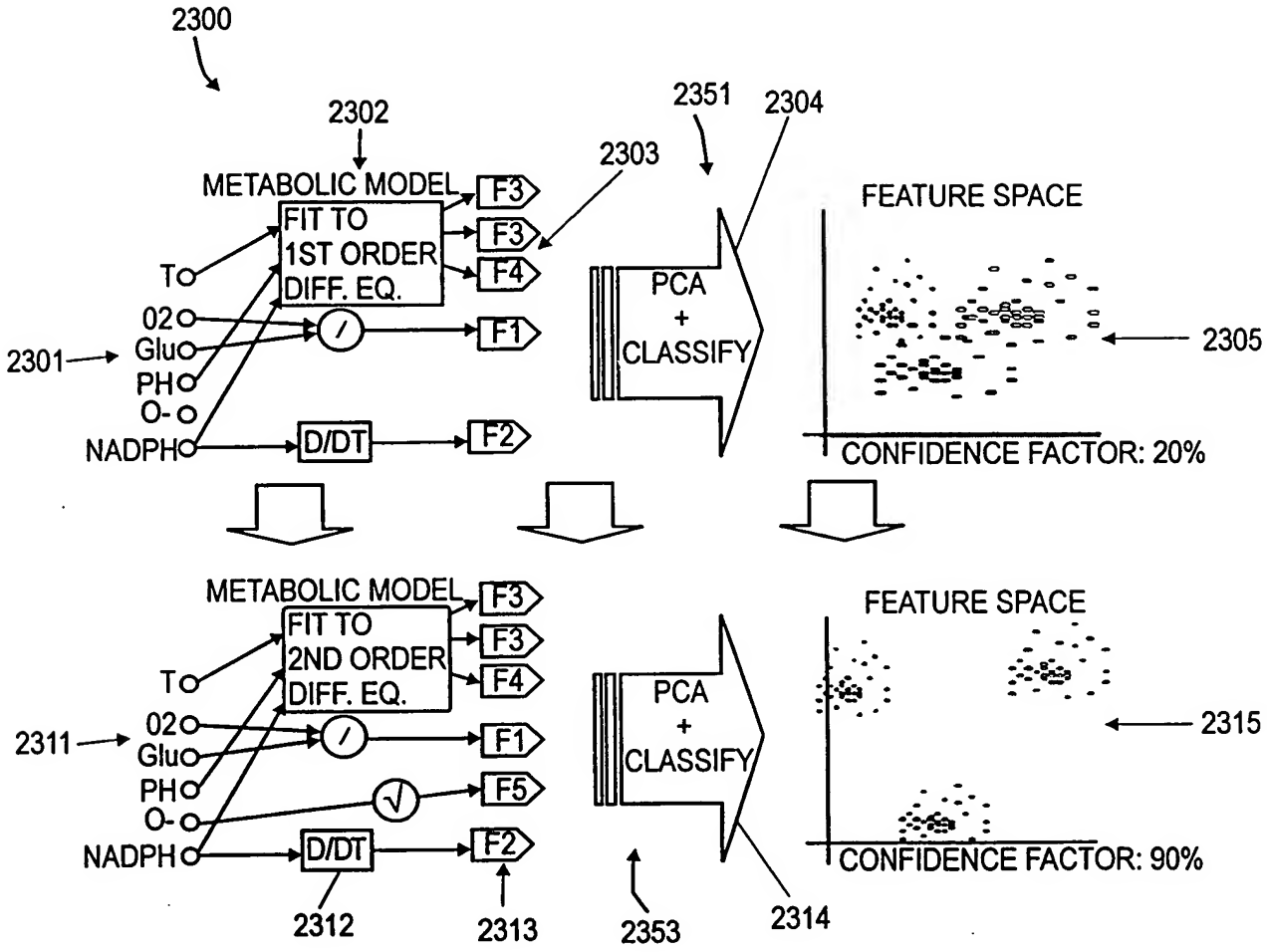
2300
2302
2351
2304
2303
METABOLIC MODEL
FIT TO
1ST ORDER
DIFF. EQ.
F3
F3
F4
F1
F2
T
02
Glu
PH
O-
NADPH
2301
D/DT
PCA
+
CLASSIFY
FEATURE SPACE
2305
CONFIDENCE FACTOR: 20%
METABOLIC MODEL
FIT TO
2ND ORDER
DIFF. EQ.
F3
F3
F4
F1
F5
F2
T
02
Glu
PH
O-
NADPH
2311
D/DT
2312
2313
2353
2314
PCA
+
CLASSIFY
FEATURE SPACE
2315
CONFIDENCE FACTOR: 90%

Fig. 23

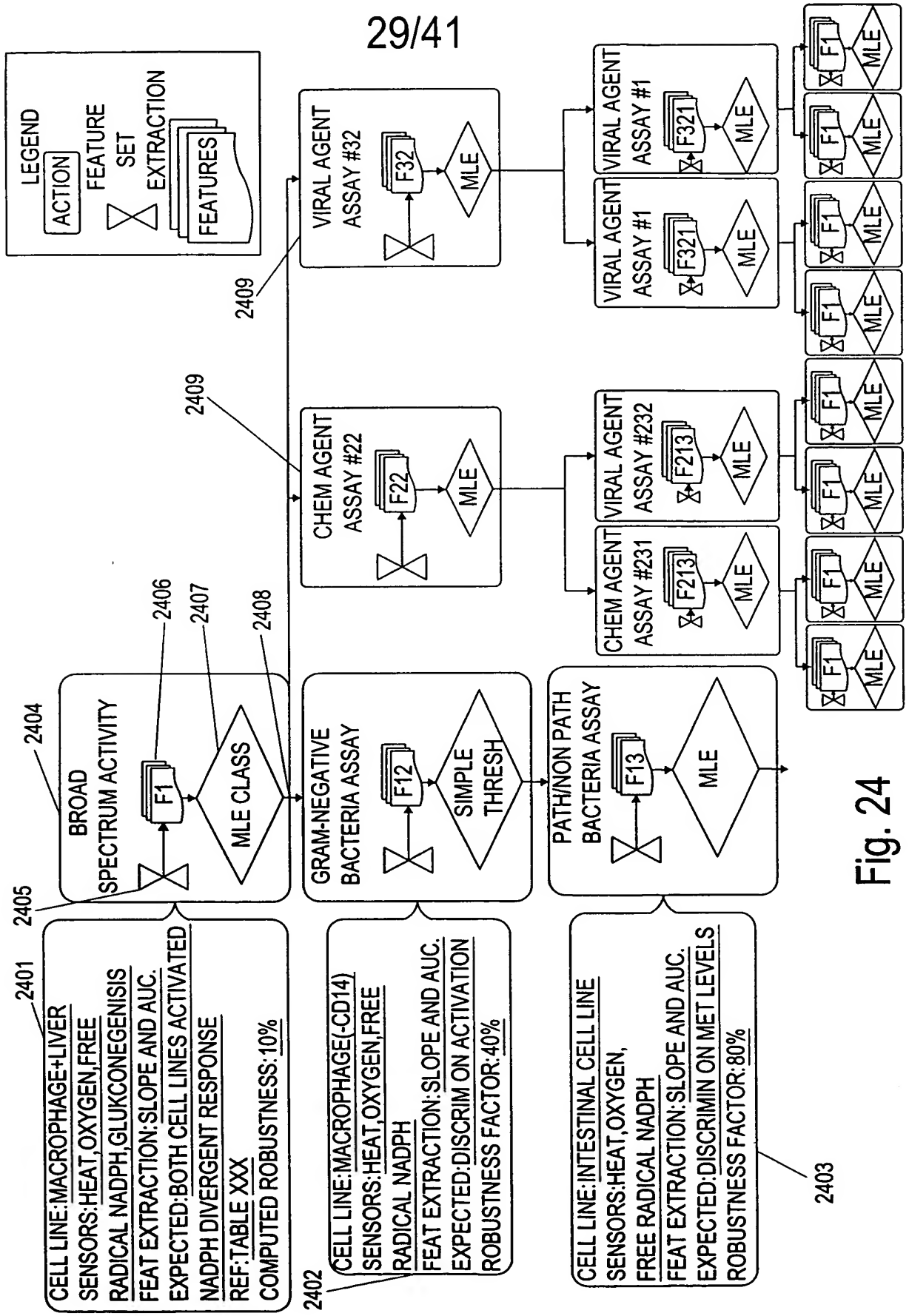
LEGEND
ACTION
FEATURE SET EXTRACTION
FEATURES
2401
2402
2403
2404
2405
2406
2407
2408
2409
CELL LINE:MACROPHAGE+LIVER
SENSORS:HEAT,OXYGEN,FREE RADICAL NADPH,GLUKCONEGENISIS
FEAT EXTRACTION:SLOPE AND AUC.
EXPECTED:BOTH CELL LINES ACTIVATED NADPH DIVERGENT RESPONSE
REF:TABLE XXX
COMPUTED ROBUSTNESS:10%
BROAD SPECTRUM ACTIVITY
F1
MLE CLASS
CELL LINE:MACROPHAGE(-CD14)
SENSORS:HEAT,OXYGEN,FREE RADICAL NADPH
FEAT EXTRACTION:SLOPE AND AUC.
EXPECTED:DISCRIM ON ACTIVATION
ROBUSTNESS FACTOR:40%
GRAM-NEGATIVE BACTERIA ASSAY
F12
SIMPLE THRESH
CELL LINE:INTESTINAL CELL LINE
SENSORS:HEAT,OXYGEN,
FREE RADICAL NADPH
FEAT EXTRACTION:SLOPE AND AUC.
EXPECTED:DISCRIMIN ON MET LEVELS
ROBUSTNESS FACTOR:80%
PATH/NON PATH BACTERIA ASSAY
F13
MLE
CHEM AGENT ASSAY #22
F22
MLE
VIRAL AGENT ASSAY #32
F32
MLE
CHEM AGENT ASSAY #231
F213
MLE
VIRAL AGENT ASSAY #232
F213
MLE
VIRAL AGENT ASSAY #1
F321
MLE
VIRAL AGENT ASSAY #1
F321
MLE
F1
MLE

Fig. 24

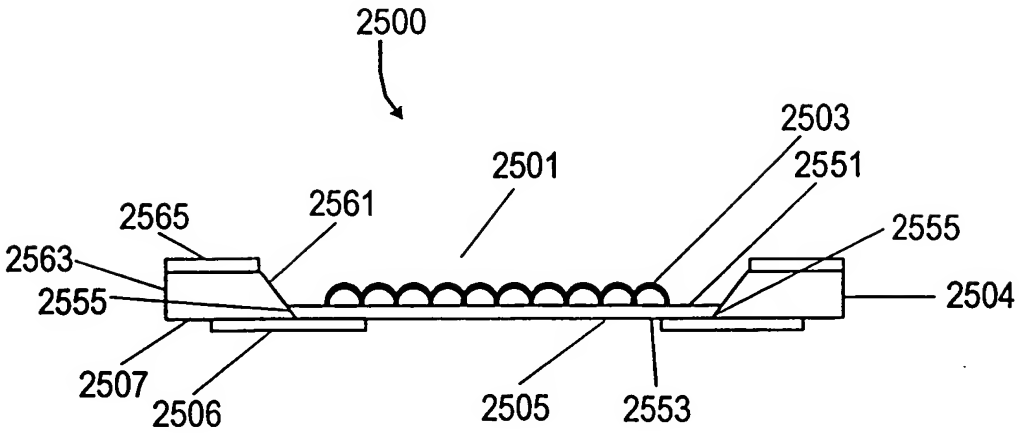

Fig. 25A

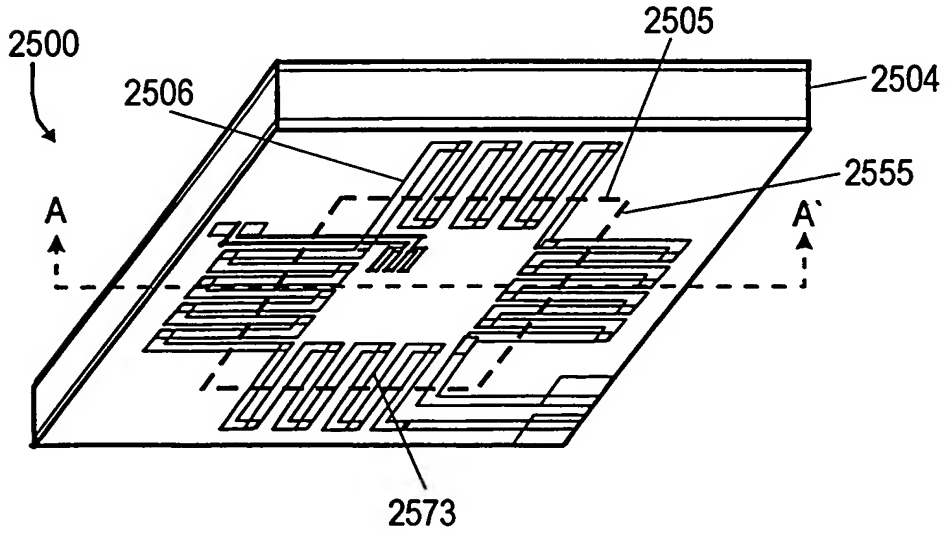

Fig. 25B

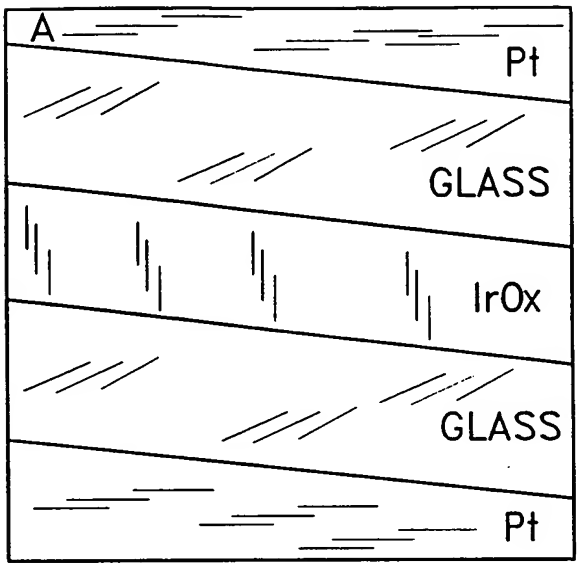

FIG.26A

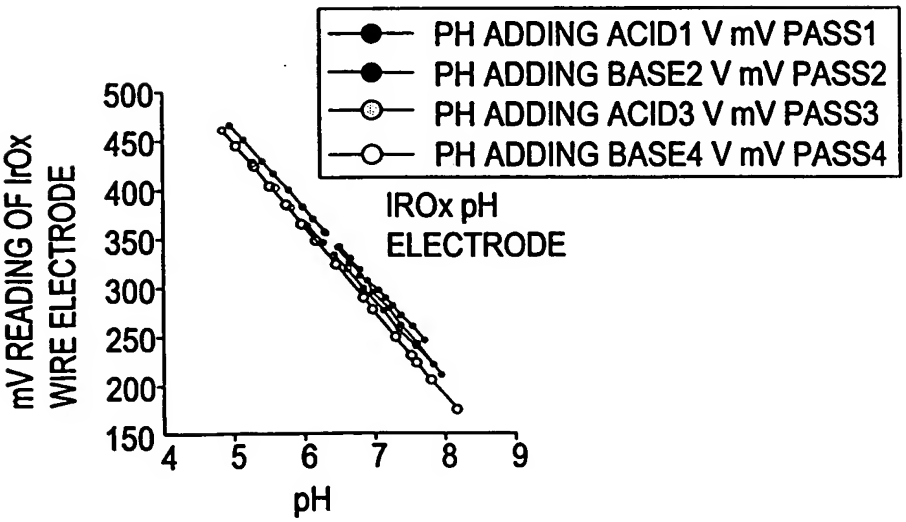

FIG.26B

10/510500

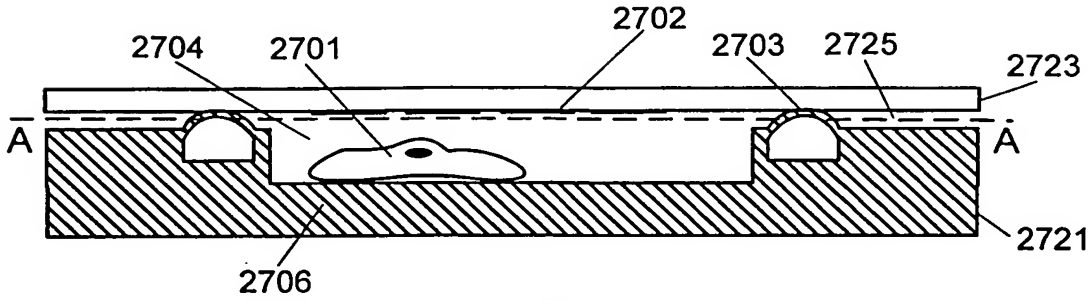

Fig. 27A

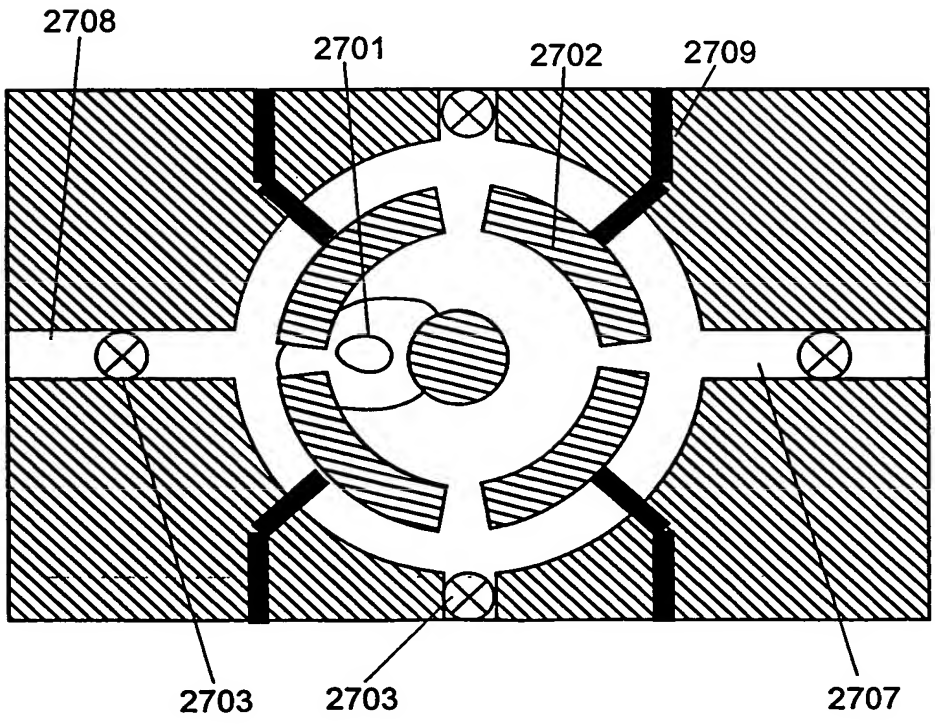

Fig. 27B

10/510500

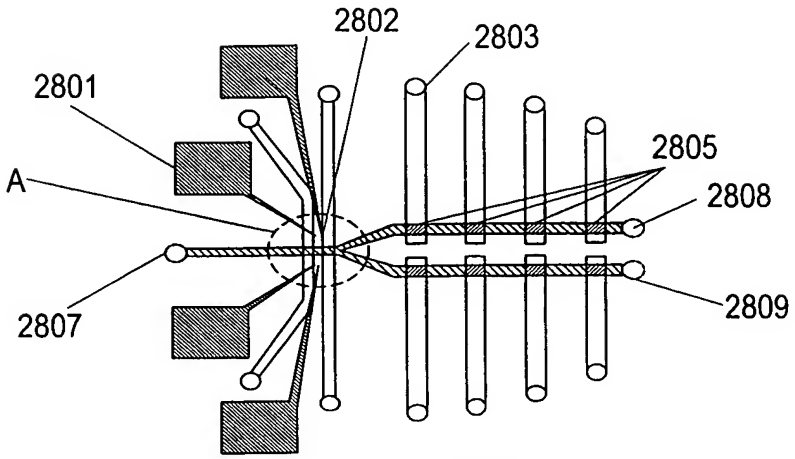

FIG.28A

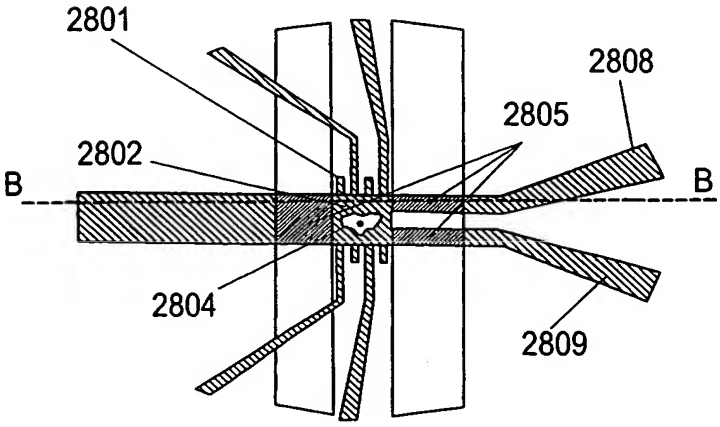

FIG.28B

10/510500

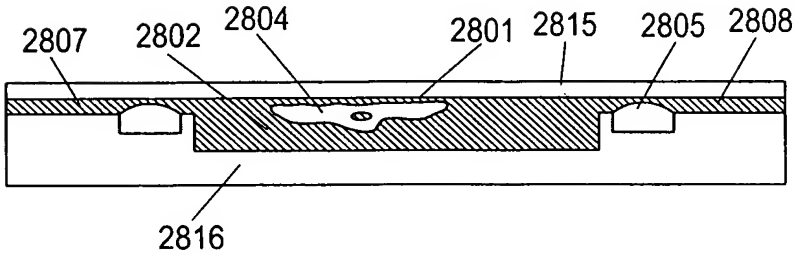

FIG.28C

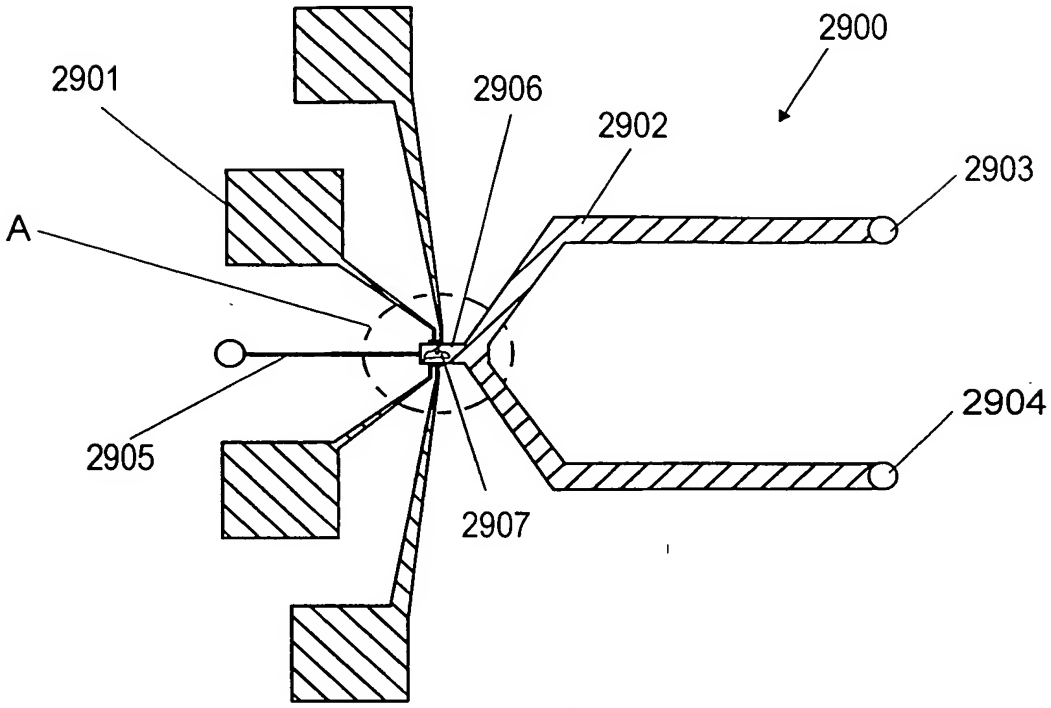

Fig. 29A

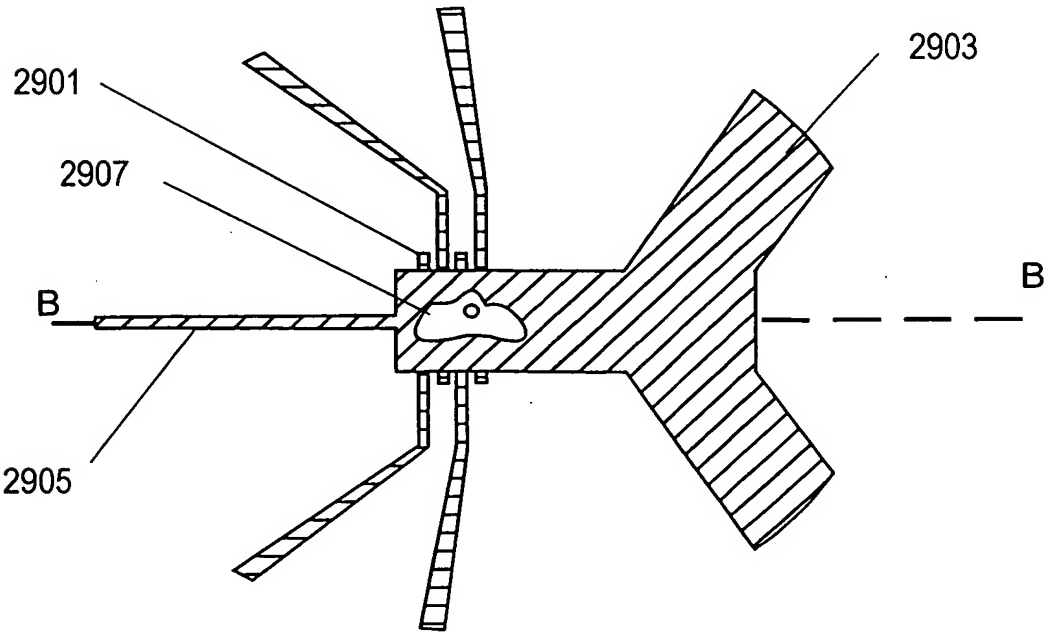

Fig. 29B

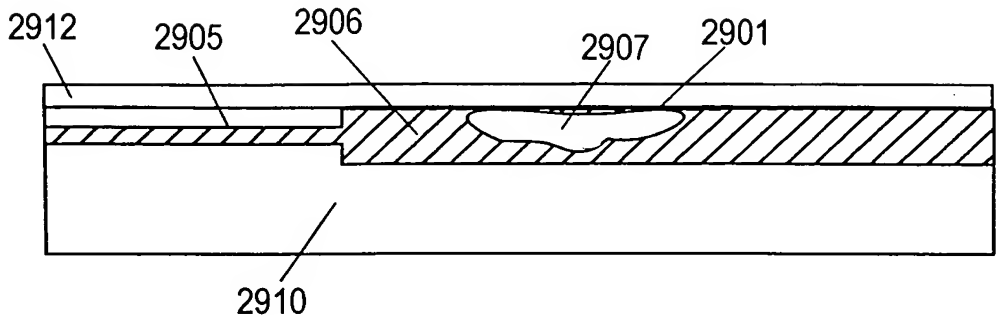

Fig. 29C

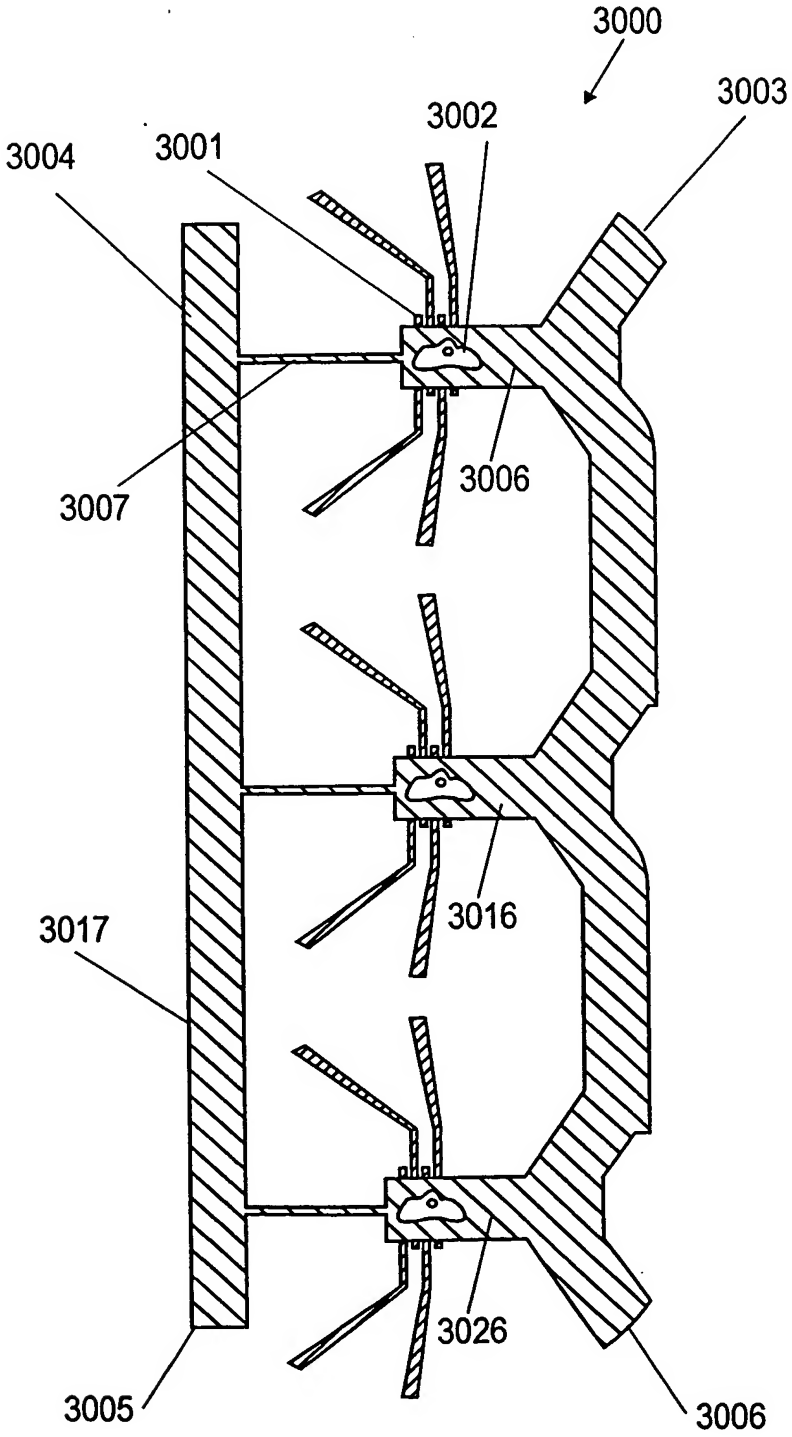

Fig. 30

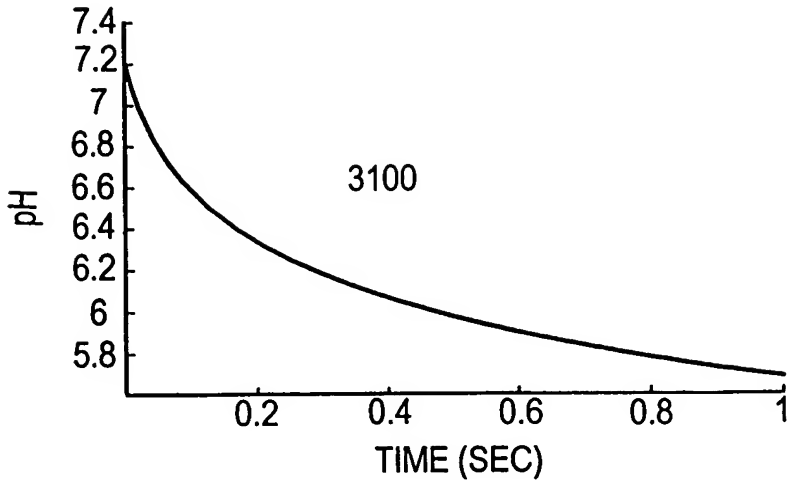

Fig. 31A

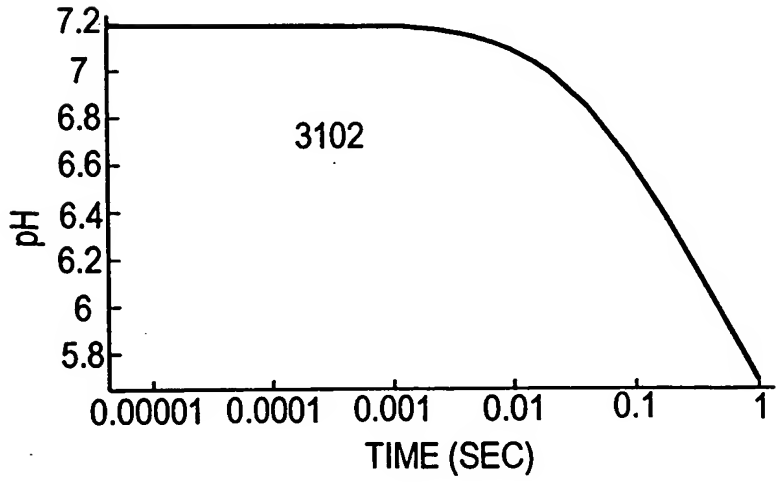

Fig. 31B

10/510500

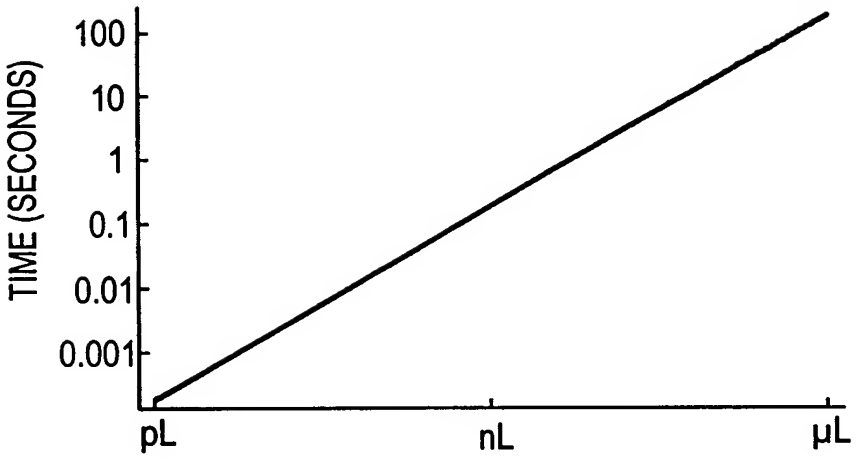

Fig. 31C

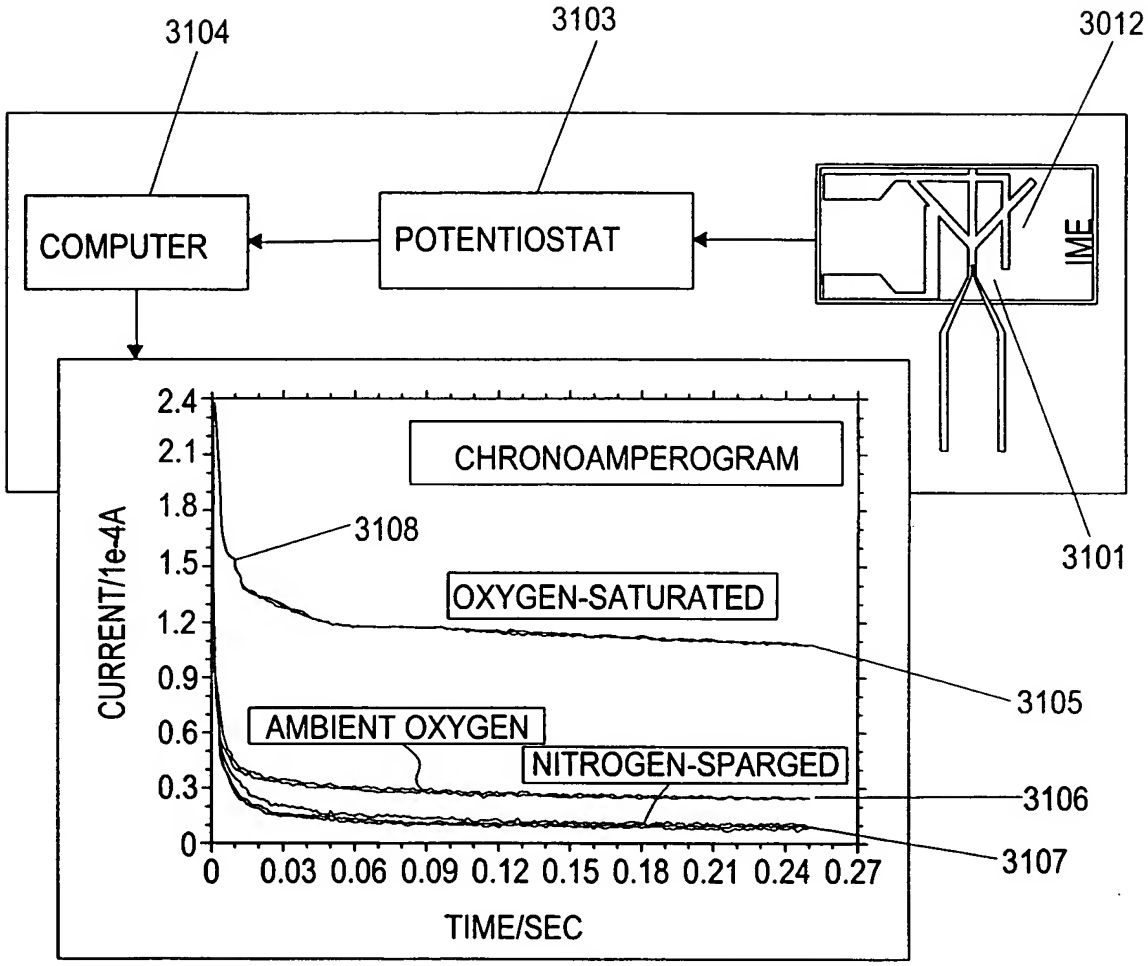
3104
3103
3012
COMPUTER
POTENTIOSTAT
IME
3101
CHRONOAMPEROGRAM
3108
OXYGEN-SATURATED
3105
AMBIENT OXYGEN
NITROGEN-SPARGED
3106
3107
CURRENT/1e-4A
2.4
2.1
1.8
1.5
1.2
0.9
0.6
0.3
0
0 0.03 0.06 0.09 0.12 0.15 0.18 0.21 0.24 0.27
TIME/SEC

Fig. 31D

10/510500

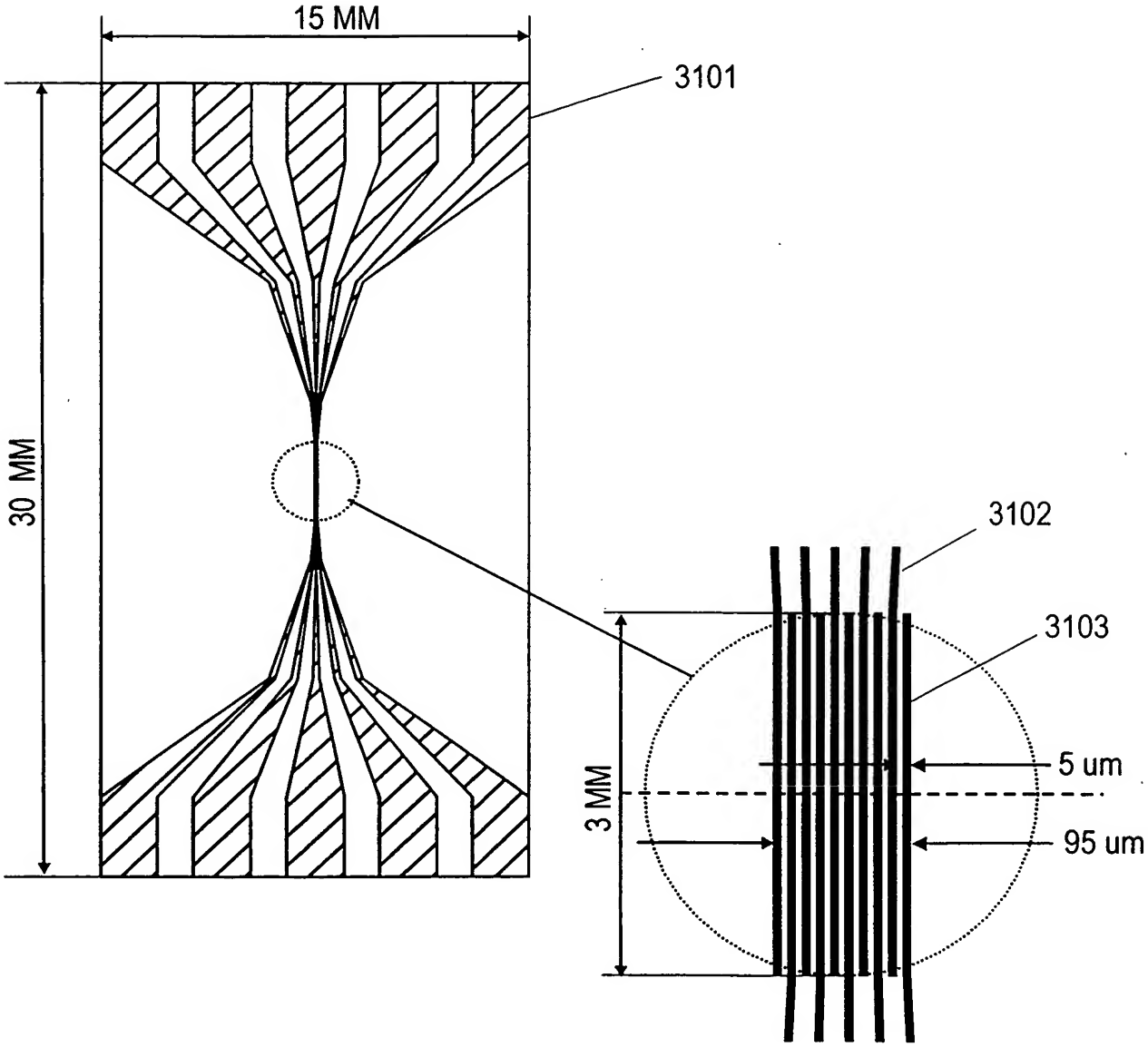

Fig. 31E